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OCTOBER 1980

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Paroxysmal Hypertension After Cardiac Surgery

Doppler Cardiac Output Measurement

Vagal Techniques for Terminating Supraventricular Tachycardia

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ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

Cardiac output and blood pressure normally increase with increasing physical activity. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[1,2]

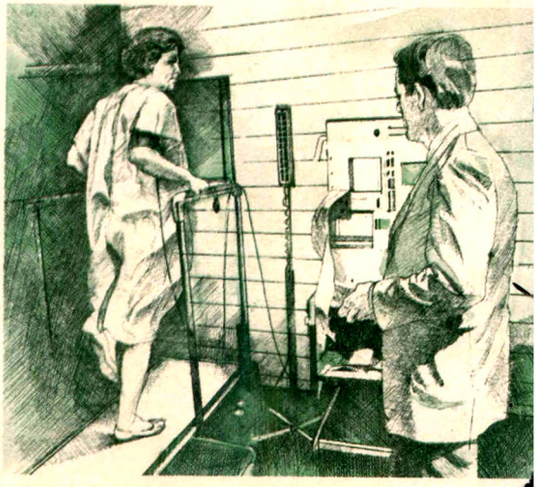
In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

Such findings can be of importance to active hypertensive patients such as the athletic individual or the person whose work requires substantial physical effort. For these and many other hypertensive patients, ALDOMET represents a logical therapeutic choice.

With ALDOMET, exercise hypotension rarely occurs. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

ALDOMET® offers many (METHYLDOPA|MSD) other important features:

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previo methyldopa therapy has been associated with live disorders. It is important to recognize that a positiv Coombs test, hemolytic anemia, and liver disord may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unles properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hyp tension by means of a graduated ergometric test, in Zanc (ed): ALDOMET® (Methyldopa | MSD) in Worldwide C Experience, West Point, PA, Merck Sharp & Dohme, 197 pp 56-63.
2. Mancia G, Ferrari A, Gregorini G, et al: Effects of trea with methyldopa on basal hemodynamics and on neural latory control, in Zanchetti A (ed): ALDOMET® (Methyldo MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.
3. Lee WR, Fox LM, Slotkoff LM: Effects of antihyperten therapy on cardiovascular response to exercise. Am J Ca 44:325-328, 1979.

For hypertension—

ALDOMET® The most prescribed nondiuretic antihypertensive in the U.S. too
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TABLETS: 500 mg, 250 mg, and 125 mg

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For a brief summary of prescribing information, please see following page.

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For hypertension—

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The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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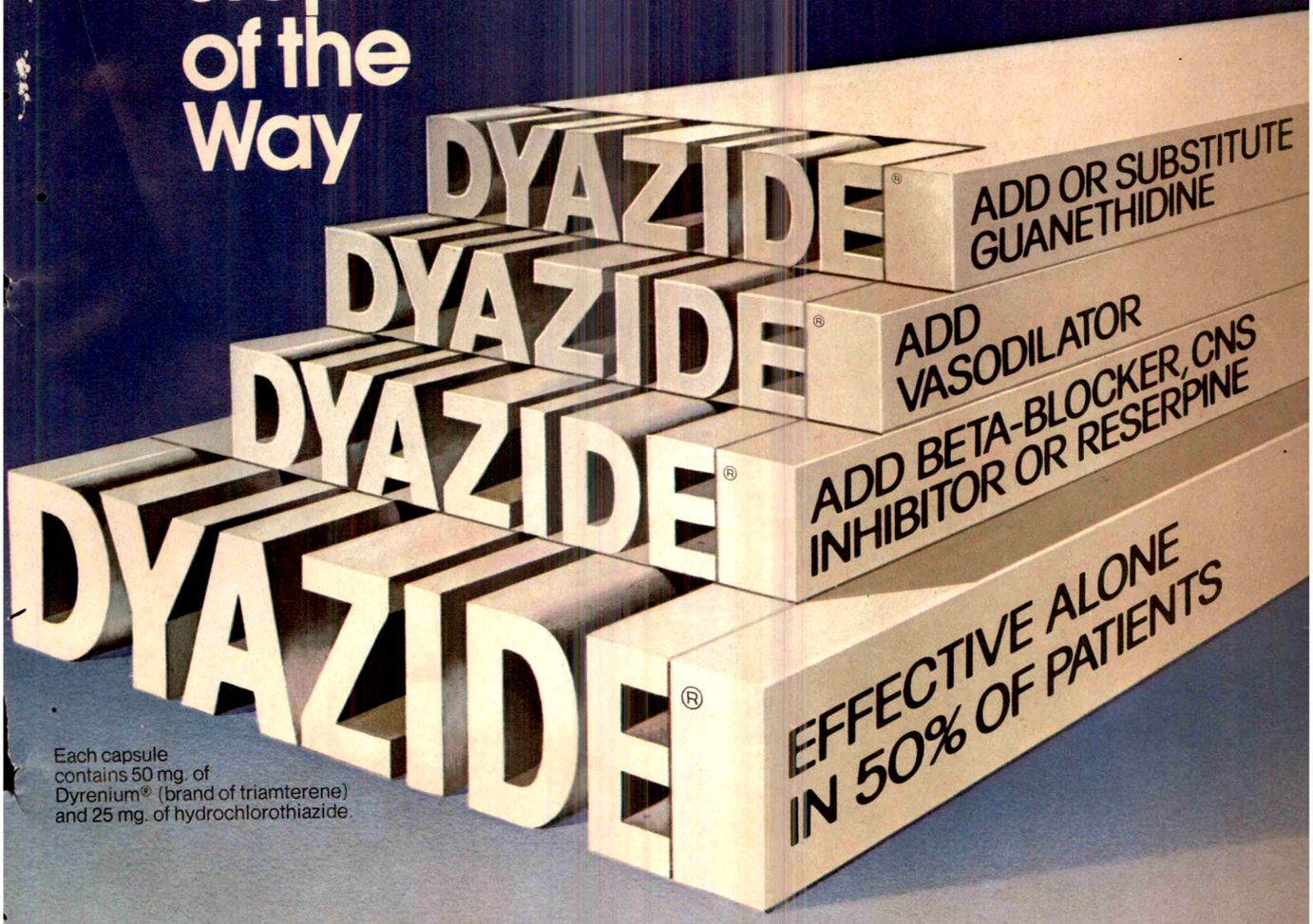
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Each capsule
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Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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dependable, prolonged protection during periods of emotional or physical exertion.

Summary Of Prescribing Information

* **Indications:** Based on a review of this drug by The National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications as follows:

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE* (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.

Duration of Effect: One to two hours.

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For patients who need K^+Cl^- one sparkles bright:

KLORVESS® EFFERVESCENT GRANULES offer SPARKLING FAST DISSOLUTION

Each packet (2.8 g) provides 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, and L-lysine monohydrochloride 0.913 g.

- **ready in *seconds* instead of minutes —fast dissolution so unique it's patented***
- **pleasant citrus flavor**
- **each packet delivers 20 mEq of potassium and chloride**
- **easily carried in patient's pocket or purse**
- **can be mixed with water or other liquid for pleasant daily dosage**
- **sugar, sodium, carbohydrate and dye free**

Give your patients the KLORVESS sparkle

Please see brief summary of prescribing information on adjoining page.

*U.S. Pat. No. 4,093,710

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26790 A

Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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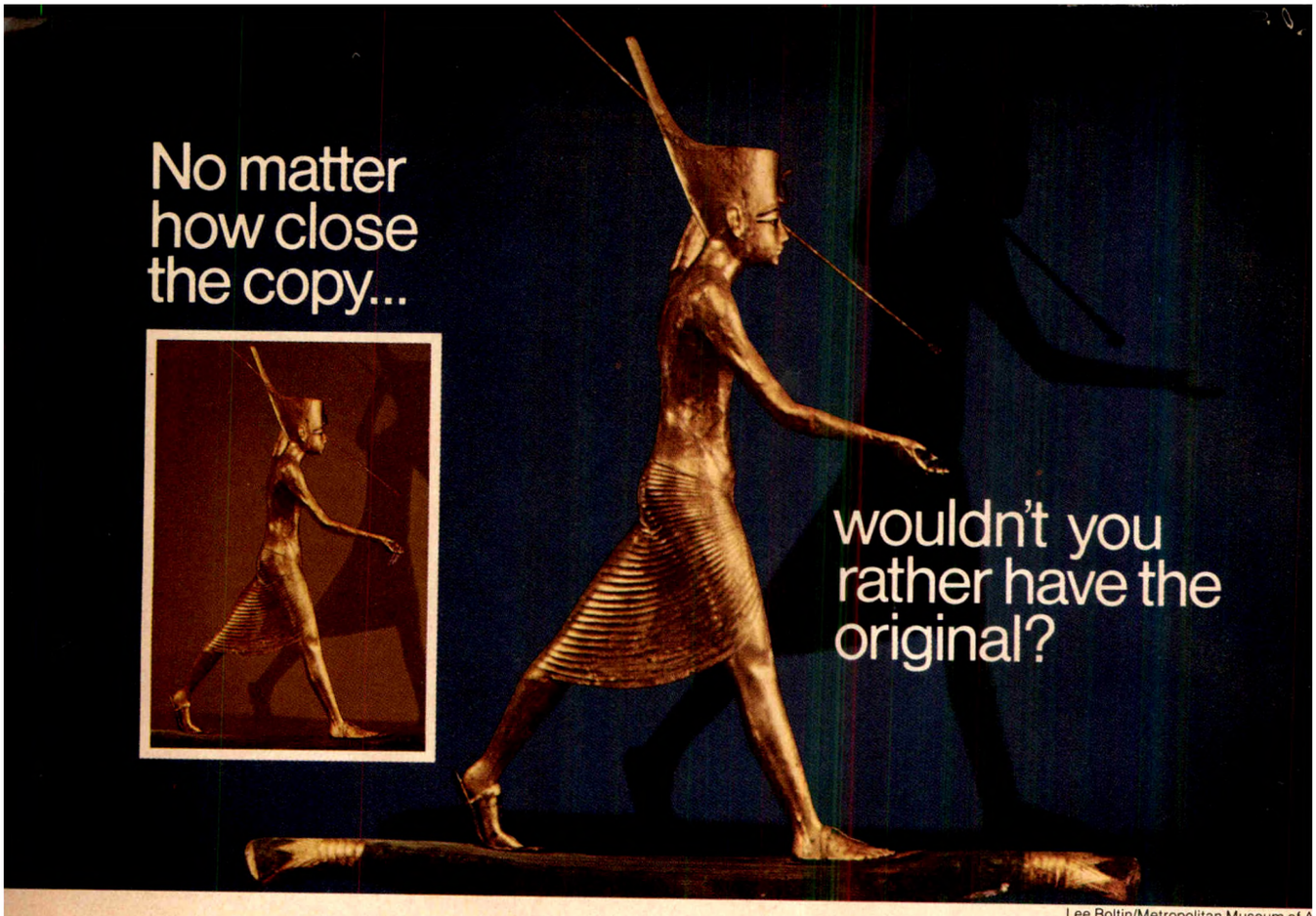
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The original dipyridamole.



Persantine®
(dipyridamole)

INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and /or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS— Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg and 75 mg

For complete details, please see the full prescribing information.

Boehringer Ingelheim Ltd.
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OCTOBER 1980

The American Journal of CARDIOLOGY®

VOLUME 46

NUMBER 4

CONTENTS

CLINICAL STUDIES

535 **Absence of Correlation Between Coronary Arterial Atherosclerosis and Severity or Duration of Diabetes Mellitus of Adult Onset**

VINCENT J. VIGORITA, G. WILLIAM MOORE and GROVER M. HUTCHINS

Correlation of the clinical and autopsy data in 185 patients with diabetes mellitus of adult onset suggests that the progression of atherosclerotic disease is unrelated to the duration or severity of the diabetes, but the larger coronary arteries in the diabetic patients are subject to more atherosclerosis than are those in nondiabetic subjects. The diabetic patients also showed an increase in angiographically determined number of diseased coronary vessels, diffuseness of coronary disease and collateralization of coronary arteries. The severity of diabetes mellitus predicted only retinopathy. These results indicate that the progress of larger vessel coronary atherosclerotic disease in diabetes mellitus of adult onset takes place independently of the progress of the diabetes itself.

543 **Clinical and Arteriographic Variables Predictive of Survival in Coronary Artery Disease**

EDWARD V. PLATIA, LOUISE GRUNWALD, E. DAVID MELLITS, JOHN O'NEAL HUMPHRIES and LAWRENCE S. C. GRIFFITH

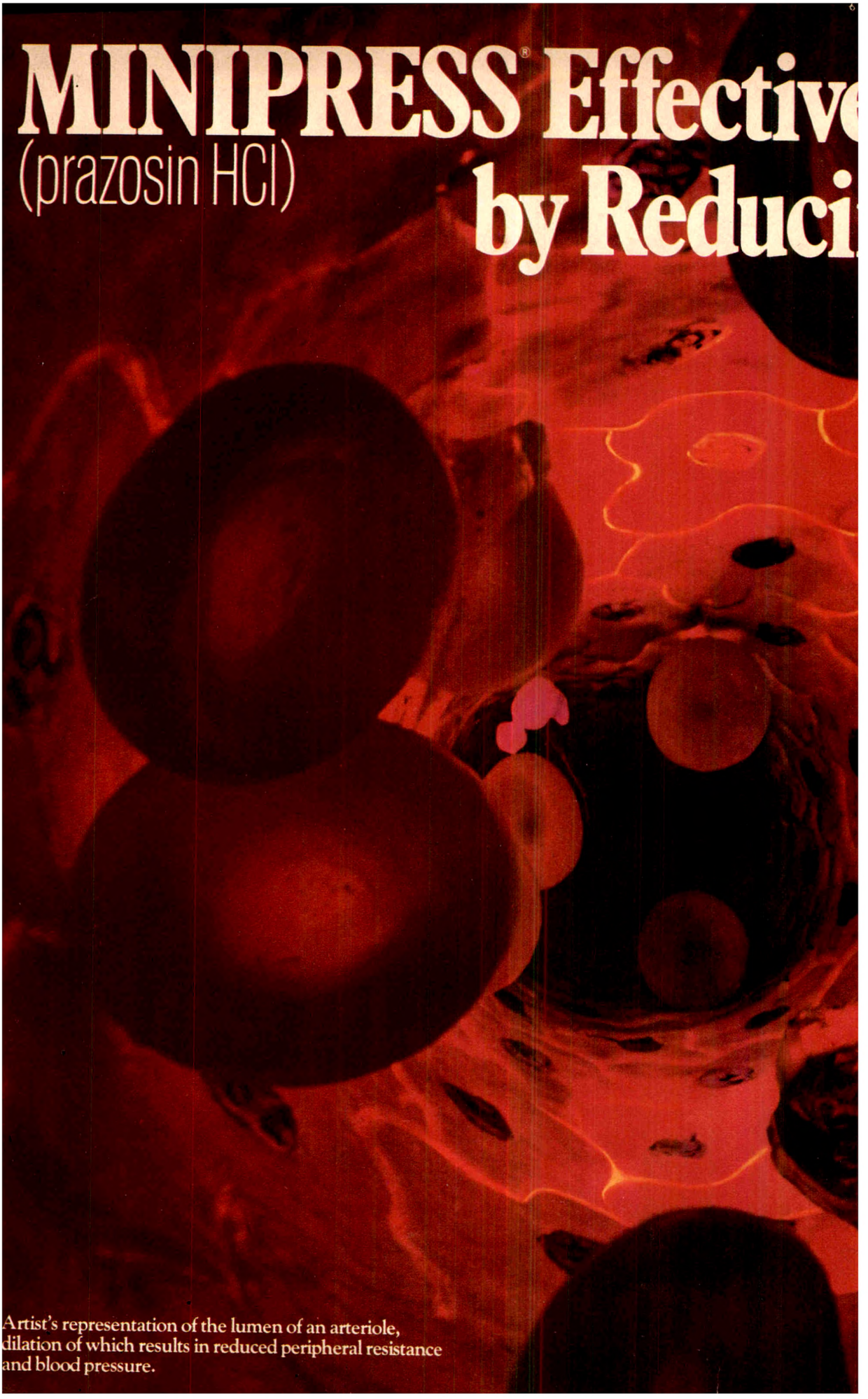
Utilizing multivariate stepwise discriminate function analysis in 90 nearly consecutive patients who underwent coronary arteriography at The Johns Hopkins Hospital between 1960 and 1961, these investigators identified the following three independent predictors of mortality: (1) the simultaneous occurrence of a narrowing in the left anterior descending and right coronary arteries; (2) prior myocardial infarction; and (3) 70 percent or greater narrowing proximal to the first anterior descending septal branch. When included, a "positive" stress electrocardiographic test also proved an independent predictor of mortality. Survival analysis showed the poorest outcome in patients with a 70 percent or greater narrowing in the proximal left anterior descending artery and a positive stress test and the best outcome in patients with similar arterial narrowing but a negative stress test.

553 **Merits of Stress Thallium-201 Myocardial Perfusion Imaging In Patients With Inconclusive Exercise Electrocardiograms: Correlation With Coronary Arteriograms**

ABDULMASSIH S. ISKANDRIAN, LOUIS A. WASSERMAN, GARY S. ANDERSON, HAMID HAKKI, BERNARD L. SEGAL and SALLY KANE

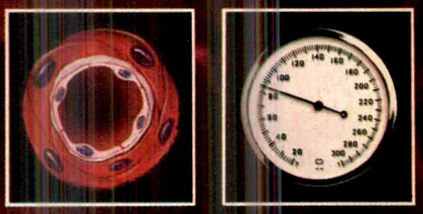
In this study of 65 patients with an inconclusive exercise electrocardiogram, exercise thallium-201 scintigraphy had a specificity of 97 percent, a sensitivity of 70 percent, a predictive positive value of 95 percent and a predictive negative value of 82 percent. With this technique the investigators were able to predict the correct diagnosis in 56 (86 percent) of the 65 patients with an inconclusive exercise electrocardiogram. In such patients exercise thallium-201 imaging appears to be more reliable when the images are abnormal than when they are normal. The high specificity and predictive accuracy of this noninasive method could reduce the need for coronary arteriography in patients with an inconclusive exercise electrocardiogram for coronary heart disease.

continued on page A16



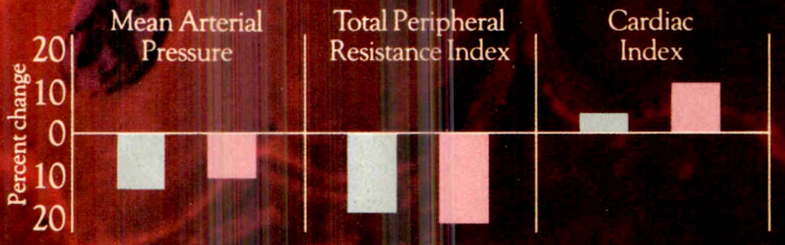
Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

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(prazosin HCl)

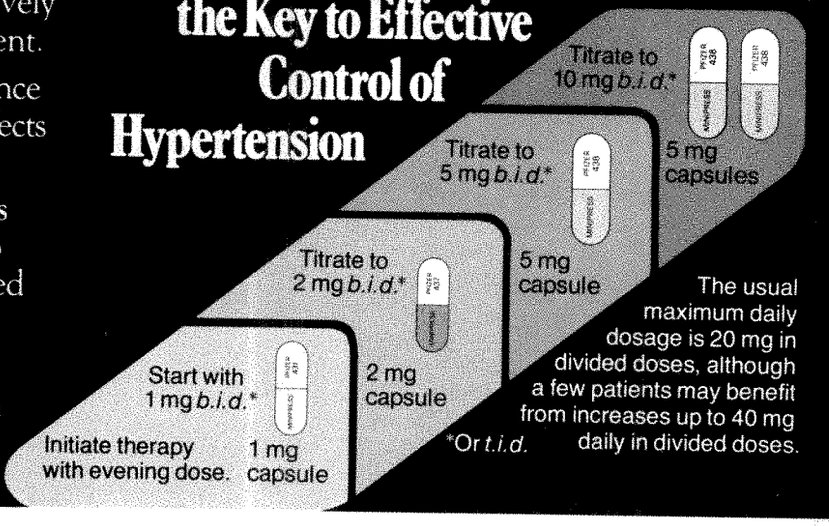
Capsules 1 mg, 2 mg, 5 mg

Please see Brief Summary on last page. © 1989 Pfizer Inc.

MINIPRESS®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure** by reducing peripheral resistance.
- **Maintains cardiac output** which allows patients to maintain an active life style.
- **Maintains renal blood flow and glomerular filtration rate** so it can be used effectively even in patients with renal impairment.
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



The usual maximum daily dosage is 20 mg in divided doses, although a few patients may benefit from increases up to 40 mg daily in divided doses.

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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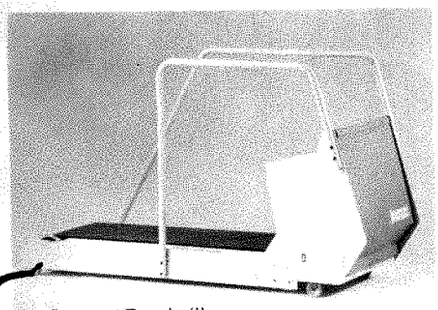
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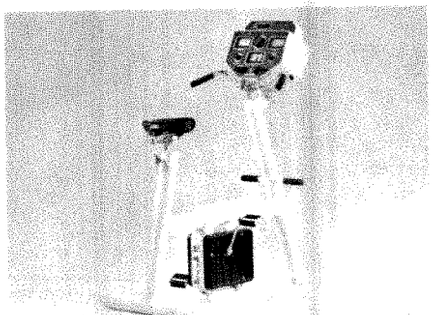
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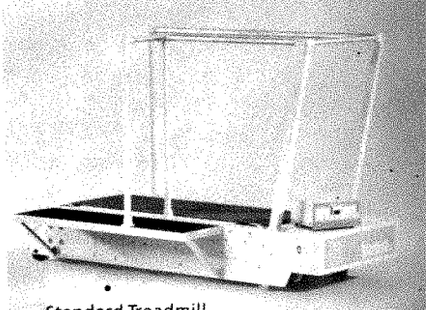
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559 **Pathogenesis of Paroxysmal Hypertension Developing During and After Coronary Bypass Surgery: A Study of Hemodynamic and Humoral Factors**

RONALD WALLACH, ROBERT B. KARP, J. G. REVES, SUZANNE OPARIL, LLOYD R. SMITH and THOMAS N. JAMES

Fifteen (54 percent) of 28 patients manifested new hypertension with increased peripheral vascular resistance and unchanged cardiac output within 1 hour after surgery. An elevation in plasma epinephrine and norepinephrine concentration, suggesting enhanced sympathoadrenal responsiveness to the challenge of cardiopulmonary bypass, was characteristic of the hypertensive group. Patients with severe angina of prolonged duration, well preserved ventricular myocardium and coronary anatomy suitable for more than three saphenous vein bypass grafts tend to become hypertensive postoperatively. The pathophysiologic mechanism of sympathetic activity in patients with new hypertension after saphenous vein bypass surgery remains uncertain.

566 **Early Results With Composite Strut Caged Ball Prostheses**

QUENTIN MACMANUS, GARY GRUNKEMEIER, LELAND HOUSMAN, CHRISTOPHER MALONEY, BRADLEY HARLAN, LOUIS LAMBERT and ALBERT STARR

Experience with 270 operative survivors of mitral valve replacement with the model 6400/10 prosthesis and 240 operative survivors of aortic valve replacement with a model 2400/10 prosthesis, all on continuous anticoagulant therapy, indicates that cloth wear and hemolysis have not been significant problems with this prosthesis. The rates of thromboembolism are comparable with those reported for xenograft bioprostheses. The composite strut valve is a durable alternative to the glutaraldehyde-preserved porcine xenograft valve in patients who are able to tolerate anticoagulant therapy.

570 **Genesis of Pericardial Knock in Constrictive Pericarditis**

THEODORE I. TYBERG, ALLAN V. N. GOODYER and RENE A. LANGOU

Supported by data from left ventriculograms, phonocardiograms and external pulse recordings in seven patients with hemodynamic and pathologic findings of constrictive pericarditis and in seven normal subjects, these investigators were able to relate pericardial knock to an abrupt plateau in the diastolic left ventricular volume curve. This relation was evident in five patients with constrictive pericarditis and the knock but absent in two patients with pericarditis and no knock. These data support the view that sudden cessation of ventricular filling generates the pericardial knock of constrictive pericarditis. Although the precise mechanism by which the sudden limitation of ventricular filling in constrictive pericarditis is converted to the sound of the pericardial knock remains to be clarified, a "water-hammer" effect or a "sail-flop" phenomenon may be responsible.

576 **Initiation and Termination of Ventricular Tachycardia by Supraventricular Stimuli. Incidence and Electrophysiologic Determinants as Observed During Programmed Stimulation of the Heart**

HEIN J. J. WELLENS, FRITS W. BÄR, JERÓNIMO FARRÉ, DAVID L. ROSS, ISAAC WIENER and EDGARD J. VANAGT

Ventricular tachycardia could be initiated by a single ventricular premature stimulus during ventricular pacing in 43 patients and in 7 (16 percent) of these same 43 patients by a single atrial premature stimulus during atrial pacing. All seven patients showed a right bundle branch block configuration of the QRS complex and a relatively slow rate during the tachycardia. In one patient a conducted atrial premature stimulus terminated the ventricular tachycardia. This study suggests that formation of an abnormal impulse at the supraventricular level may play a more important role than previously realized in the initiation of ventricular tachycardia and that in some patients initiation of ventricular tachycardia by a conducted supraventricular impulse will occur only if the premature impulse is aberrantly conducted through the ventricle.

continued on page A20

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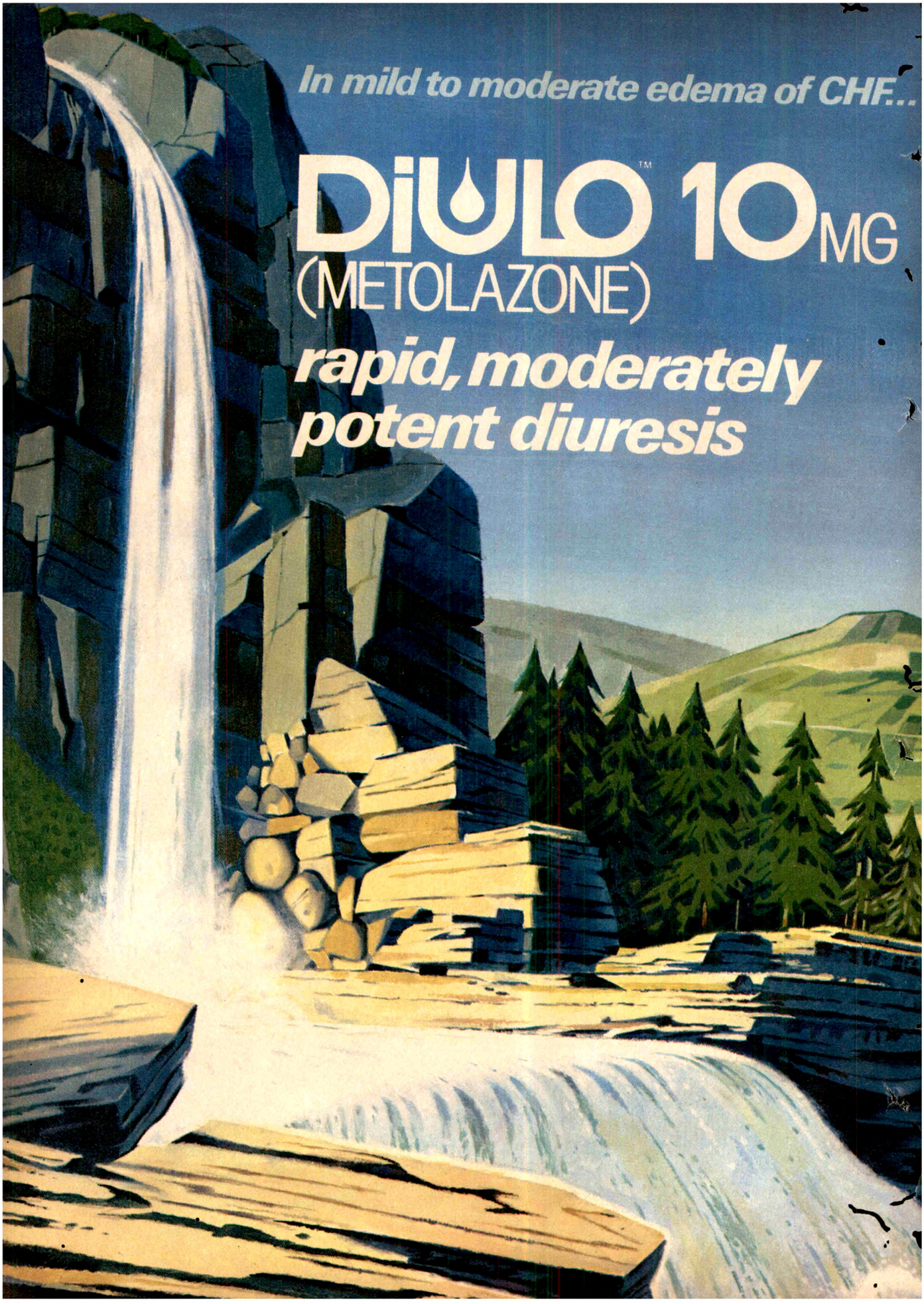
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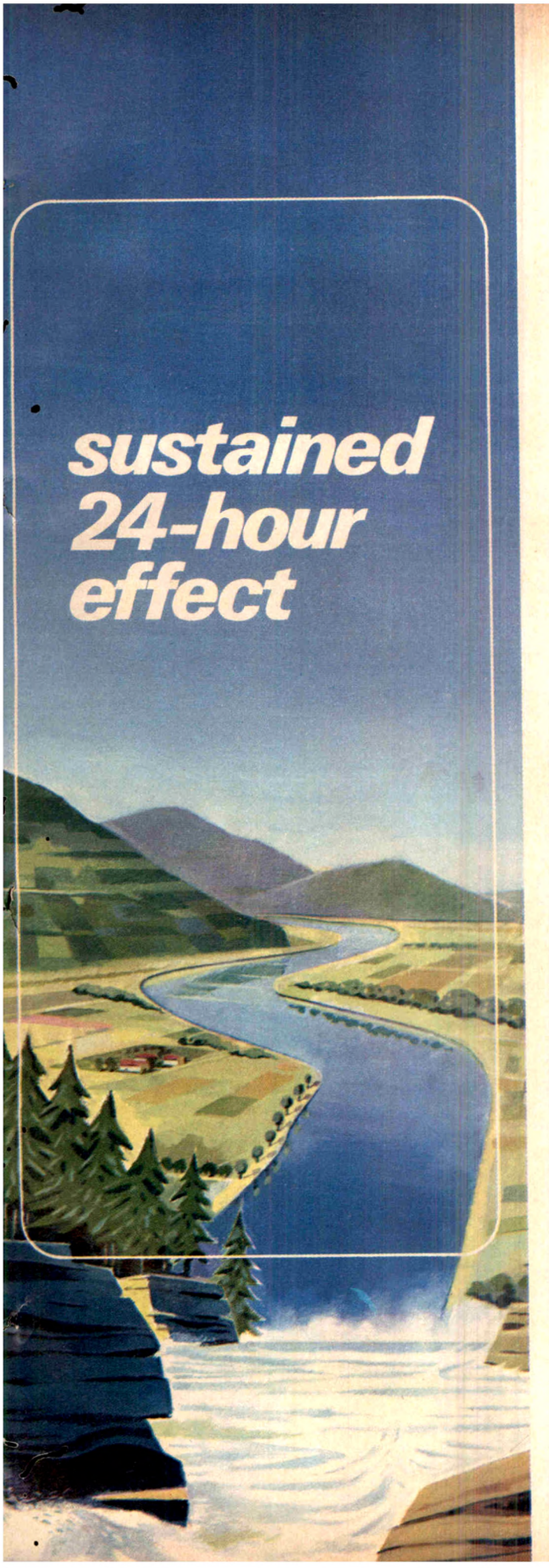
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With Diulo 10 mg, your patient with chronic CHF benefits from effective diuretic action. But unlike those receiving more potent diuretics, patients receiving Diulo are not "wrung out" in two or three hours.

Although the conditions of some patients can be adequately controlled with a 5-mg dose of Diulo, one 10-mg tablet daily can provide effective diuresis around the clock in your patients with CHF, including those with paroxysmal nocturnal dyspnea.

DIULO™ (metolazone) 2½-mg., 5-mg. and 10-mg. tablets *Before prescribing, see complete prescribing information. The following is a brief summary:* ***Indications:*** *Diulo (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease.* ***Contraindications:*** *Anuria, hepatic coma or precoma; allergy or sensitivity to metolazone.* ***Warnings:*** *In theory, cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When added to other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to pregnant women or those of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Metolazone appears in the breast milk. Not recommended for pediatric use.* ***Precautions:*** *Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance, hyponatremia, hypochloremic alkalosis and hypokalemia. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur.* ***Adverse Reactions:*** *Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks.* ***Usual Initial Once-Daily Dosages:*** *Mild to moderate essential hypertension – 2½ to 5 mg.; edema of cardiac failure – 5 to 10 mg.; edema of renal disease – 5 to 20 mg. Dosage adjustment is usually necessary during the course of therapy.* ***How Supplied:*** *Tablets, 2½, 5 and 10 mg.; in bottles of 100 and 500, and cartons of 100 unit-dose individually blister-sealed tablets.*

SEARLE

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CONTENTS

EXPERIMENTAL STUDIES

583 Kinetics of Antifibrillatory Effects of Bretylium: Correlation With Myocardial Drug Concentrations

JEFFREY L. ANDERSON, EUGENE PATTERSON, MARILYN CONLON, STANISLAW PASYK, BERTRAM PITT and BENEDICT R. LUCCHESI

These data confirm the excellent antifibrillatory effects of bretylium in the dog heart and emphasize the importance of tissue pharmacokinetics in determining its behavior. Serum bretylium concentration decreased rapidly after intravenous injection, whereas myocardial concentrations increased gradually, peaking at 1.5 to 6 hours in both open and closed chest dogs. Electrophysiologic and antifibrillatory effects paralleled myocardial rather than serum drug kinetics with peak effects at 3 to 6 hours. The average increase in the ventricular fibrillation threshold exceeded 12-fold after administration of 6 mg/kg of the drug (2 minutes to 12 hours). These results suggest a need during the clinical use of this drug for repeated acute drug dosing and allowance of greater time after acute bretylium administration before assuming drug failure.

593 Myocardial Effects of Long-Term Cigarette Smoking: Relative Roles of Carbon Monoxide and Nicotine

S. SULTAN AHMED, CHRISTOS B. MOSCHOS, HENRY A. OLDEWURTEL and TIMOTHY J. REGAN

In this well designed beagle study the effects of long-term cigarette use on the myocardium appear to depend predominantly on nicotine rather than on carbon monoxide. Carboxyhemoglobin did not differ among beagles smoking three cigarettes of low or high nicotine content, either in the immediate postsmoking or late period. In dogs smoking low nicotine cigarettes for 18 months there were no abnormalities of myocardial performance or composition. The nicotine users exhibited a significant decrease in diastolic compliance during volume expansion, a decrease in the basal contractility indexes and increases in the collagen content of the myocardium. Serum lipids were unchanged in the long-term smokers and in the group receiving nicotine.

599 Electrophysiologic Effects of Imipramine and Doxepin on Normal and Depressed Cardiac Purkinje Fibers

F. JAMES BRENNAN

In this study the direct electrophysiologic actions of imipramine and doxepin on isolated canine Purkinje fibers are shown to be similar. Moderately depressed fibers are more sensitive than normal fibers to certain of these effects. Both imipramine and doxepin reduced conduction velocity and failed to alter the refractory periods of the depressed fibers whereas at the same concentration in normal fibers they caused no change in conduction velocity but shortened the refractory periods. The different incidence rates of arrhythmias and conduction disturbances associated with their clinical use is probably not due to differences in their direct electrophysiologic effects on the ventricular specialized conduction system, but may be due to the generally lower plasma drug levels in patients receiving doxepin than in those receiving imipramine.

METHODS

607 Transcutaneous Method of Measuring Doppler Cardiac Output—I. Comparison of Transcutaneous and Juxta-aortic Doppler Velocity Signals With Catheter and Cuff Electromagnetic Flowmeter Measurements in Closed and Open Chest Dogs

JOHN R. DARSEE, J. RONALD MIKOLICH, PAUL F. WALTER and ROBERT C. SCHLANT

This study of 20 closed and open chest dogs demonstrates the usefulness of the transcutaneous Doppler method of measuring cardiac output by multiplying the 1 minute sum of Doppler velocity integrals in systole by the cross-sectional area of the proximal aorta. The results showed a close similarity between Doppler signals and electromagnetic waveforms and a close similarity between Doppler and thermodilution values for cardiac output except at heart rates above 160 beats/min. Application of this method to clinical use in human beings, although promising, requires further study to develop a method for measuring the cross-sectional area of the aorta and accounting for systolic change.

continued on page A26

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TO 4½ MILLION HYPERTENSIVE PATIENTS, THIS IS USUALLY THE ONLY SIGN THAT INDERAL® IS WORKING.

(PROPRANOLOL HCl)

A modest reduction in pulse rate: usually the first sign that INDERAL is at work.

Mode of action, yes. Side effect, no. Because it is generally accepted that even heart rates as low as 50 to 55 beats per minute, in otherwise asymptomatic patients, are not usually a cause for concern. The real side effects* associated with INDERAL occur so infrequently that today over 4½ million hypertensive patients are doing well on regimens built around INDERAL.

To their physicians, the signs are even more encouraging...

because INDERAL, alone or in combination with other agents, has established a remarkable record of blood pressure control. Another encouraging sign: increased dosage usually does not produce proportional decreases in heart rate.

Proper patient selection is important: INDERAL should be employed only in the absence of congestive heart failure, sinus bradycardia, or heart block greater than first degree.*

But in most patients, the initial signs of its effect will be reflected in subsequent signs of effectiveness: significantly lowered blood pressure.

Effective in b.i.d. dosage

For most patients twice-daily dosing of INDERAL is effective in maintaining blood pressure reduction throughout the day. Some patients on lower doses may experience a modest rise in blood pressure at the end of a 12-hour interval. Larger doses, or t.i.d. dosing, should re-establish control.



At the heart of well-tolerated antihypertensive therapy

INDERAL®

(PROPRANOLOL HCl)

B.I.D.

FOR HYPERTENSION

40 mg and 80 mg tablets

*Please see the following page for brief summary of prescribing information on warnings, including avoidance of abrupt withdrawal, contraindications, and adverse reactions.

P24, 120

INDERAL® (PROPRANOLOL HCl)

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
Inderal® BRAND OF
propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved in the antihypertensive action are (1) decreased cardiac output; (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension
INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION

ORAL

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 40 mg INDERAL twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual dosage is 160 to 480 mg per day. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12 hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3 times daily therapy may achieve better control.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

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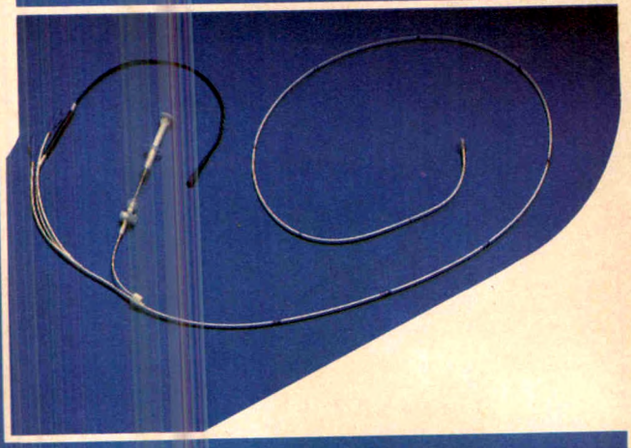
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613 **Transcutaneous Doppler Method of Measuring Cardiac Output—II. Noninvasive Measurement by Transcutaneous Doppler Aortic Blood Velocity Integration and M Mode Echocardiography**

JOHN R. DARSEE, PAUL F. WALTER and DONALD O. NUTTER

Noninvasive measurement of cardiac output by transcutaneous Doppler aortic blood velocity integration and M mode echocardiography is useful and practical for measuring changes in cardiac output in patients with acute myocardial infarction. Results are poorer at heart rates exceeding 150 beats/min. Advantages of the Doppler method over catheterization techniques for the repeated measurement of cardiac output include the use of a single unit on multiple patients, none of the risks of indwelling catheters, no necessity for blood samples or expansion of the intravascular volume, greater safety, and availability for use by nurses and technicians.

619 **Improved Diagnostic Accuracy of Thallium-201 Stress Test Using Multiple Observers and Criteria Derived From Interobserver Analysis of Variance**

ROBERT D. OKADA, CHARLES A. BOUCHER, HOWARD K. KIRSHENBAUM, FRED G. KUSHNER, H. WILLIAM STRAUSS, PETER C. BLOCK, KENNETH A. McKUSICK and GERALD M. POHOST

These results demonstrate considerable interobserver variance in the overall interpretation of the thallium stress test. Use of the standard criteria and four observers produced complete agreement on the overall diagnosis in 58 percent, partial agreement in 26 percent and complete disagreement in 16 percent of cases. Use of the interobserver variance analysis criteria increased complete agreement to 70 percent and reduced partial agreement and complete disagreement to 22 and 8 percent, respectively. Interpretation by multiple observers increases the diagnostic accuracy of the thallium stress test. Averaging of the multiple observer scores and interpretation of the averaged scores using the average criteria appears more useful than interpretation by simple consensus.

625 **Echocardiographic Features of Atrioventricular and Ventriculoatrial Conduction**

MASAHITO NAITO, LEONARD S. DREIFUS, T. JOSEPH MARDELLI, CHIN C. CHEN, DANIEL DAVID, ERIC L. MICHELSON, VAL MARCY and JOEL MORGANROTH

Simultaneous hemodynamic and M mode and two dimensional echocardiographic correlates of changes in cardiac performance resulting from changes in atrioventricular (A-V) conduction patterns. By scanning the A-V interval from +100 to −100 ms in the presence of A-V and V-A sequential packing, these investigators observed progressive decreases in systolic blood pressure, cardiac output and left ventricular size together with increases in left atrial sizes. The findings suggest that echocardiography can provide insight into the mechanisms responsible for the hemodynamic disorders that result from various patterns of A-V conduction or that occur during supraventricular arrhythmias.

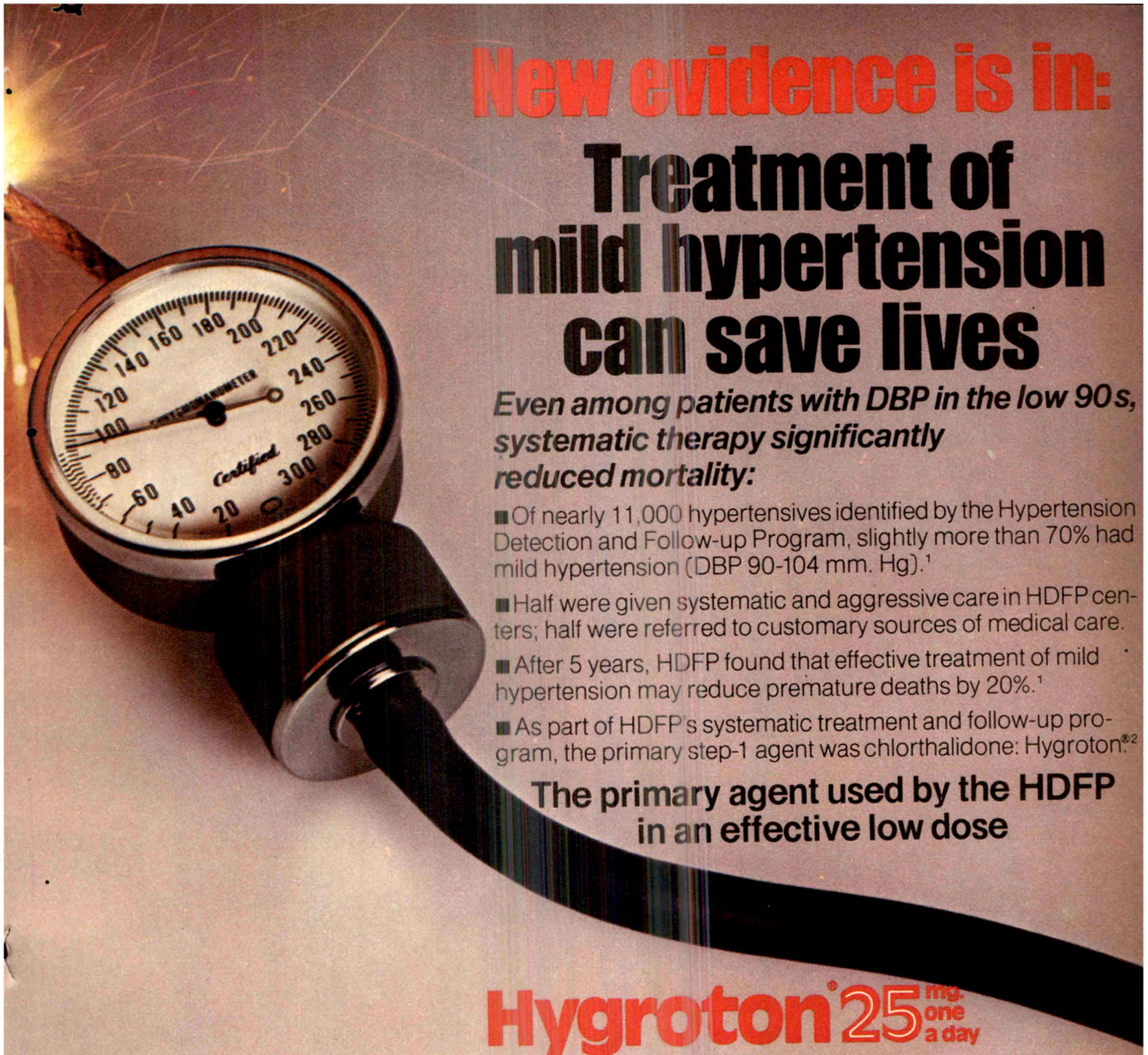
PEDIATRIC CARDIOLOGY

635 **Long-Term Evaluation (12 to 22 Years) of Open Heart Surgery for Tetralogy of Fallot**

VALENTIN FUSTER, DWIGHT C. McGOON, MARGARET A. KENNEDY, DONALD G. RITTER and JOHN W. KIRKLIN

This 12 to 22 year long-term evaluation of 396 hospital survivors of 475 patients who underwent repair of tetralogy of Fallot shows an excellent late clinical result in 87 percent. A less than excellent result in the remaining 13 percent was caused by late mortality in 7 percent, need for reoperation in 4 percent and the development of symptoms in 2 percent. Most late deaths and complications appeared within 2 years of operation, and accelerating deterioration in late results did not occur as the follow-up period extended beyond 2 years. Late mortality and reoperation were the two major reasons for the decrease in excellent results during the first 2 postoperative years. Right ventricular outflow abnormalities were the cause of death in seven patients (1.5 percent). Fourteen of the 19 patients required reoperation because of a residual or recurrent ventricular septal defect.

continued on page A30



New evidence is in:

Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).[1]
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.[1]
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The primary agent used by the HDFP in an effective low dose

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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And...DAIG CORPORATION, will continue its commitment to the development and improvement of cardiac pacing leads and accessories for the world pacemaker market.

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ALL DAIG/MEDCOR Pulse Generators are backed by a Lifetime Replacement Credit Agreement.

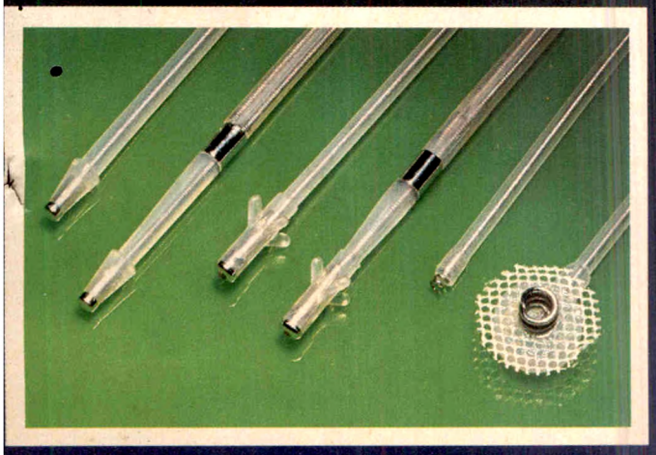


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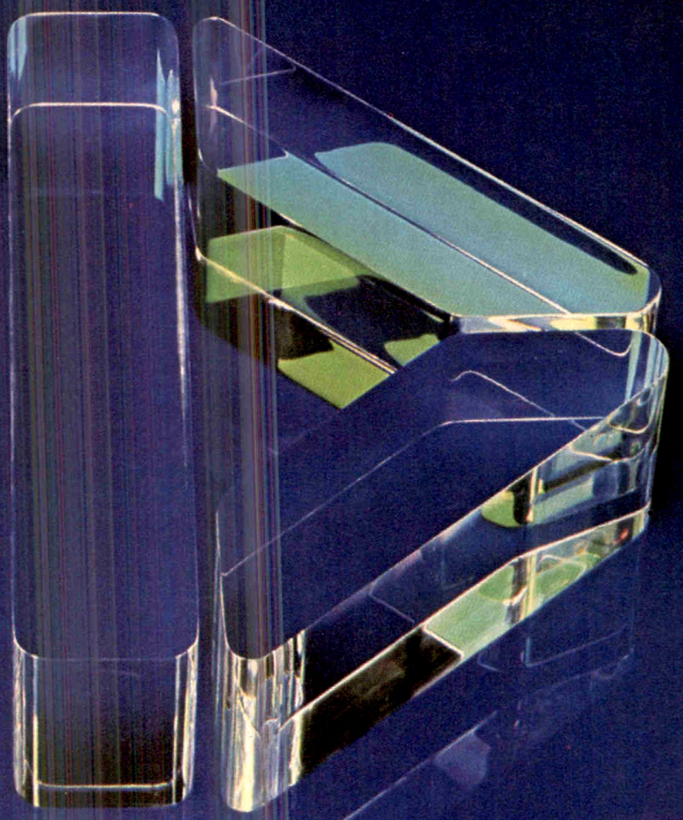
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643 **Cardiac Malformations in the Velocardiofacial Syndrome**

DENNISON YOUNG, ROBERT J. SHPRINTZEN and ROSALIE B. GOLDBERG

The findings of velopharyngeal insufficiency, a submucous or overt cleft of the secondary palate, similar facies, learning disabilities and congenital cardiovascular anomalies whose occurrence as single or combined lesions exceeds the expected incidence in children with congenital heart disease constitute the newly designated velocardiofacial syndrome. Observations in 23 patients with this syndrome and their families indicate an unusual conformity of cardiac involvement and suggest the possibility of autosomal dominant or X chromosome-linked dominant transmission in some. Etiologic heterogeneity cannot be ruled out and the possible teratogenic effects of progestional agents given during the early first trimester of pregnancy or of exposure to anesthetic gases during pregnancy are possible but unproved.

EPIDEMIOLOGY

649 **Prevalence of Coronary Heart Disease in the Framingham Offspring Study: Role of Lipoprotein Cholesterols**

PETER W. WILSON, ROBERT J. GARRISON, WILLIAM P. CASTELLI, MANNING FEINLEIB, PATRICIA M. McNAMARA and WILLIAM B. KANNEL

In 43 of the 1,312 men aged 35 to 54 years in the Framingham Offspring Study with clinically recognized coronary heart disease at the initial examination the prevalence of coronary heart disease was strongly associated with age, smoking, high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol using univariate analyses. After multivariate analysis of the data, age, smoking, HDL and LDL cholesterol retained their significant association with coronary heart disease. Both HDL and LDL cholesterol are strongly and independently associated with the prevalence of coronary heart disease; the level of very low density lipoprotein cholesterol makes no statistically significant independent contribution. The total cholesterol/HDL ratio offers the clinician a useful index to associate lipid values with coronary disease.

REPORTS ON THERAPY

655 **Vagal Techniques for Termination of Paroxysmal Supraventricular Tachycardia**

MENASHE B. WAXMAN, ROBERT W. WALD, ARJUN D. SHARMA, FELIX HUERTA and DOUGLAS A. CAMERON

In 68 consecutive patients with paroxysmal supraventricular tachycardia 57 episodes were terminated with carotid sinus pressure alone or after pretreatment with edrophonium, 5 episodes with the Valsalva maneuvers and 6 with phenylephrine. Phenylephrine evoked the greatest increase in vagal tone; the Valsalva maneuver was more potent than carotid sinus pressure. These results confirm that maneuvers that reflexly increase vagal tone can rapidly, safely and consistently terminate paroxysmal supraventricular tachycardia. Apart from drugs that specifically reduce sympathetic tone or enhance vagal tone, reassurance, sedation and the recumbent position may exert similar effects and facilitate termination of tachycardia. Oral therapy with antisympathetic drugs like propranolol, or enhancement of vagal tone by digitalis, will increase the success and ease of termination of the arrhythmia.

665 **Effect of Drugs in the Wolff-Parkinson-White Syndrome. Importance of Initial Length of Effective Refractory Period of the Accessory Pathway**

HEIN J. J. WELLENS, FRITS W. BÄR, WILLEM R. M. DASSEN, PEDRO BRUGADA, EDGARD J. VANAGT and JERÓNIMO FARRÉ

These electrophysiologic observations in 59 patients with the Wolff-Parkinson-White syndrome indicate the importance of the initial value of the effective refractory period of the accessory pathway in determining the effect

continued on page A37

QUICK QUIZ

Fig. 1

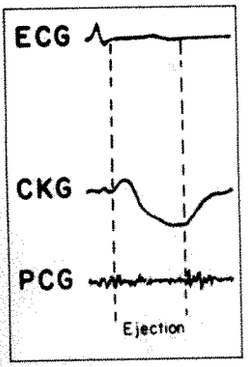


Fig. 2

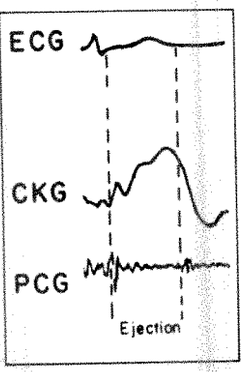


Fig. 3

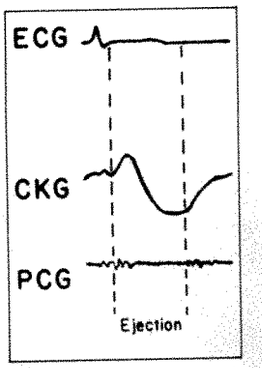
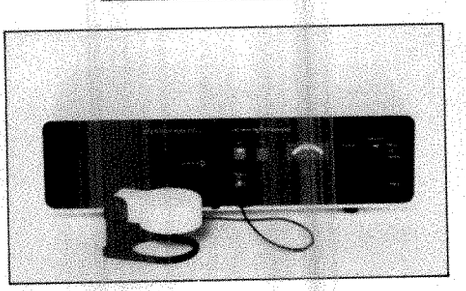


Fig. 4



I. Figure 1 is a pre-stress CKG™ (Cardiokymograph) tracing of the left ventricle (V3 position), it demonstrates:*

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

II. Figure 2 is a two minute post-stress CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

III. Figure 3 is a thirty minute post-stress resting CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

IV. Figures 1, 2 and 3, taken together, demonstrate:

- ☐ A. stress induced ventricular wall motion abnormalities consistent with ischemia
- ☐ B. normal ventricular wall motion

V. According to recently published[1] data, the CKG (Cardiokymograph) stress test is:

- ☐ A. 98% sensitive—98% specific
- ☐ B. 59% sensitive—69% specific
- ☐ C. 74% sensitive—95% specific
- ☐ D. 40% sensitive—60% specific

VI. Figure 4 is a photograph of:

- ☐ A. CKG/700 (Cardiokymograph)
- ☐ B. a noninvasive device that provides an analog representation of wall motion
- ☐ C. a low cost, simple device to be used in conjunction with stress testing to enhance diagnostic accuracy
- ☐ D. all of the above

REFERENCE

(1) Silverberg R A, Diamond G A, Vas R, Tzivoni D, Swan H J C, Forrester J S. Noninvasive Diagnosis of Coronary Artery Disease: The Cardiokymographic Stress Test. Circulation, Vol. 61, No. 3, pgs. 579-589.

™CKG is a trademark of Cardiokinetics Inc. *Patent Pending

For additional bibliography call or write

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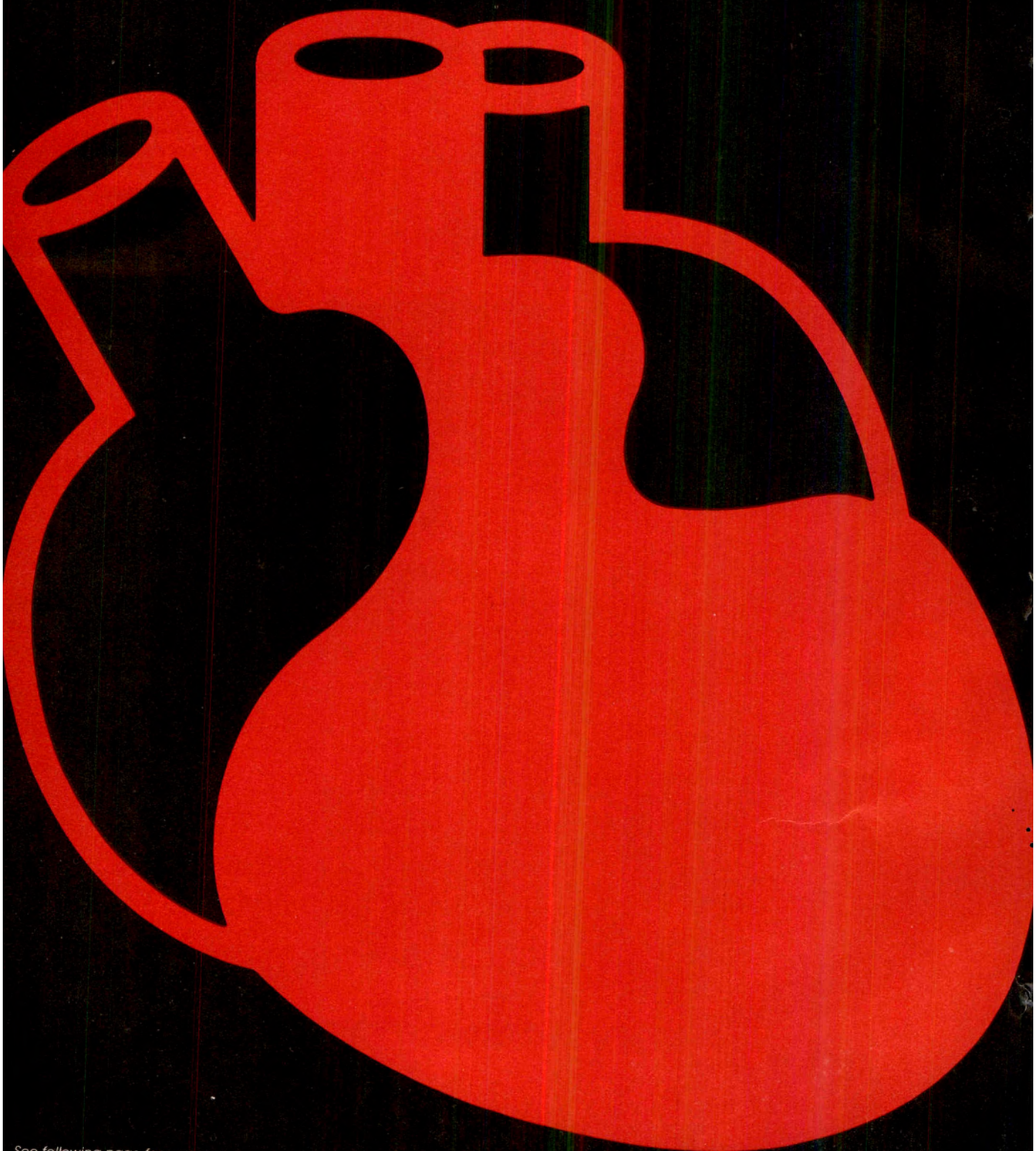
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QUICK QUIZ—ANSWERS

I. A. normal systolic inward motion **II.** C. holosystolic outward motion **III.** A. normal systolic inward motion **IV.** A. stress induced ventricular wall motion abnormalities consistent with ischemia **V.** C. 74% sensitive – 95% specific **VI.** D. all of the above

Dobutrex®
Dobutamine HCl

For Short-Term
Inotropic Support in Patients with
Low-Output Cardiac Failure



See following page for summary of prescribing information.

Selectively Increases
Myocardial Contractility
with Consistent
Hemodynamic Improvements

Dobutrex®
Dobutamine HCl



For I.V. Injection
250 mg* in 20-ml-size vials
* Equivalent to dobutamine

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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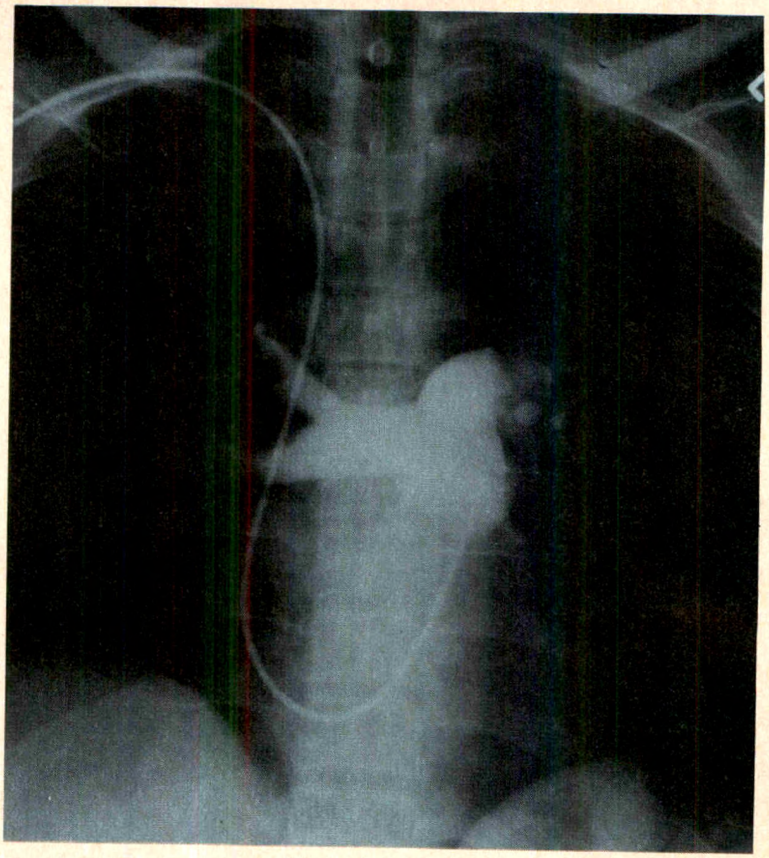
Lilly

Additional information available to the profession on request.

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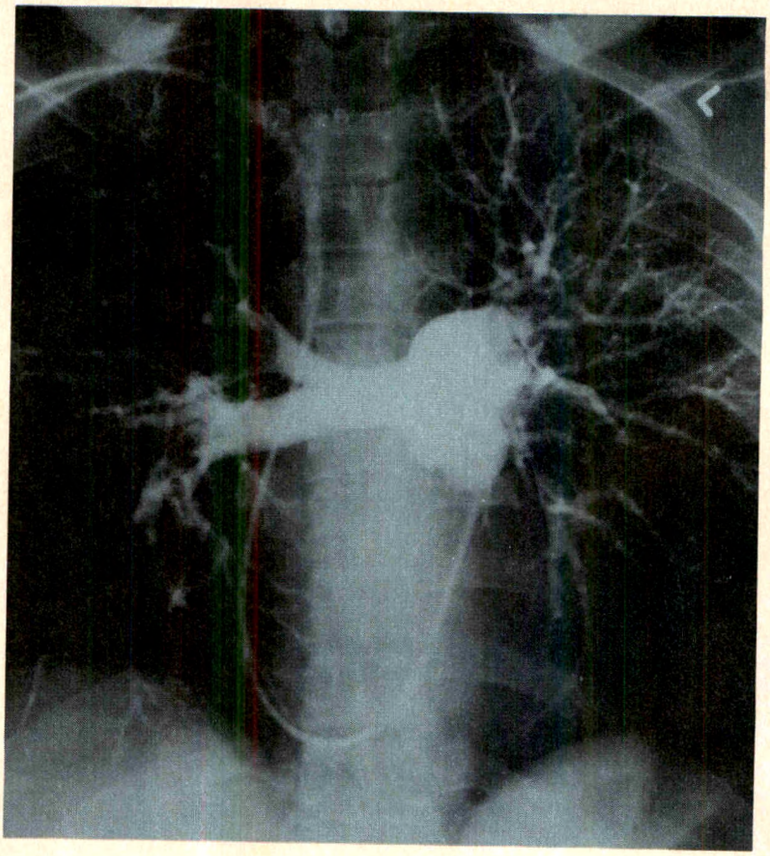
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Abbokinase®

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250,000 I.U. per vial

The direct action thrombolytic agent for the management of acute massive pulmonary embolism

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Please see following page for Brief Summary.

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Abbokinase®
Urokinase for Injection

Brief Summary

ABBOTT

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ABBOKINASE (urokinase for injection) should only be used by physicians with wide experience in the management of thrombotic disease in hospitals where the recommended clinical and laboratory monitoring (see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION) can be performed.

When considering treatment with urokinase, the physician should carefully assess the overall clinical status and history of the patient. The hemostatic capability of the patient is more profoundly altered and bleeding more frequent with urokinase therapy than with heparin or oral coumarin anticoagulant therapy. When bleeding occurs it is also more severe and more difficult to manage. The potential risk of serious hemorrhage relative to such factors as age, physical condition, and underlying bleeding tendency of the patient (as described under WARNINGS and PRECAUTIONS) should be weighed against the potential benefits of treating the patient with urokinase.

INDICATIONS

Pulmonary Embolism

ABBOKINASE (urokinase for injection) is indicated in adults:

for the lysis of acute massive pulmonary emboli, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels.[8]

for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures.

The diagnosis should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be instituted as soon as possible after onset of pulmonary embolism, and no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements demonstrate a more rapid improvement during the first 24 hours of therapy than with heparin therapy (Table I).[7-9] However, it has not been established that treatment with urokinase decreases morbidity or mortality, when compared to heparin therapy alone.

TABLE I

	UPET*		USPET**	
	Heparin	12-Hour Urokinase	12-Hour Urokinase	24-Hour Urokinase
Change in angiographic severity score based on 4-point system	0.54	1.78	1.66	1.76
Decrease in relative percentage perfusion defect on lung scans	8.3	24.1	20	29.2
Change in pulmonary artery pressure (mm Hg)	−1.1	−6.2	−7.28	−7.53
Change in cardiac index (l/min/m²)	−0.05	+0.02	+0.06	+0.30

*Urokinase pulmonary embolism trial.
**Urokinase-streptokinase pulmonary embolism trial.

Evaluations were obtained between 18 and 30 hours after the start of therapy. After several days, there were no differences between the results in the heparin treated patients and those receiving urokinase.

CONTRAINDICATIONS — Because thrombolytic therapy increases the risk of bleeding, urokinase is contraindicated in the following situations:

1. Surgery within ten days. Liver or kidney biopsy, lumbar puncture, thoracentesis or paracentesis, extensive or multiple cutdowns should be considered surgical procedures.
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days of the post-partum period.
7. Ulcerative colitis, diverticulitis or an actively bleeding lesion (or one with a significant potential for bleeding) of the gastrointestinal or genitourinary tract.
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
10. Uncontrolled hypocoagulable state, including one that may be caused by a coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, or another purpuric or hemorrhagic disorder.
11. Chronic lung disease with cavitation, e.g., tuberculosis.
12. Subacute bacterial endocarditis or rheumatic valvular disease.
13. Recent cerebral embolism, thrombosis or hemorrhage. Treatment with urokinase is contraindicated for at least two months after cerebral embolism, thrombosis or hemorrhage because patients with cerebral infarction remain at risk of bleeding into the infarcted tissue.
14. Any other condition in which bleeding might constitute a significant hazard or be particularly difficult to manage because of its location.

The conditions listed above should not be regarded as absolute contraindications. Rather, the risk of hemorrhage must be weighed carefully against the anticipated benefits of urokinase therapy in an individual patient and the benefits and risks associated with the use of urokinase should be compared to the benefits and risks associated with other forms of therapy.

WARNINGS

Bleeding

Activation of the fibrinolytic system with urokinase results in a more profound alteration of the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The aim of urokinase therapy is the production of sufficient amounts of plasmin for the lysis of intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example, at sites of needle punctures, are also destined for lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is high during thrombolytic therapy. Unnecessary handling of the patient should be avoided. Strict attention should be given to this section and the CONTRAINDICATIONS section in order to minimize the risk of bleeding.

Because of the high risk of hematoma formation, intramuscular injections must be avoided during urokinase therapy, as with heparin therapy. Bleeding at sites of recent invasive procedures may occur. Hence, arterial invasive procedures must also be avoided before and during treatment with urokinase. Should an arterial puncture be ***absolutely*** necessary, the femoral artery must be avoided and the radial or brachial artery used. It should be done carefully by a physician experienced in such a procedure. Pressure should be applied for at least 15 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding. Also, venipunctures should be performed as carefully and infrequently as possible. If the bleeding from an invasive site is not serious, treatment may be continued with appropriate clinical observation. Local measures, i.e., pressure, should be initiated immediately.

Spontaneous bleeding from internal sites (not accessible for pressure application) may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic defects, e.g., patients with histories suggestive of prior bleeding problems, with or without demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. Such patients should be assessed carefully before initiating treatment with urokinase.

In addition to its fibrinolytic action, plasmin also degrades fibrinogen, Factor V, Factor VIII, and other proteins. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect. Bleeding may be difficult to control because of this anticoagulant effect.

Should serious spontaneous bleeding occur, the infusion of urokinase should be terminated immediately, and treatment instituted as described under ADVERSE REACTIONS.

Predisposition to Cerebral Embolism

Treatment with urokinase of patients with atrial fibrillation or other conditions in which there is possible risk of cerebral embolism may be hazardous because of the risk of bleeding into the infarcted area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase is not recommended and may be hazardous. Before starting urokinase in patients being treated with heparin, the effects of heparin should be allowed to diminish with time. As a general rule, a thrombin time of ***less than twice*** the normal control value is adequate for starting urokinase infusions safely. Similarly, heparin should not be started following urokinase therapy until the thrombin time has returned to ***less than twice*** the normal control value.

Rethrombosis has been observed after termination of urokinase treatment. In order to minimize this risk, the use of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

See CONTRAINDICATIONS.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

PRECAUTIONS

Drug Interactions

Concurrent use of drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided. The interaction of ABBOKINASE (urokinase for injection) with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time should be measured prior to starting urokinase. (See WARNINGS.) Similarly, the thrombin time should be monitored following urokinase therapy prior to instituting heparin. (See DOSAGE AND ADMINISTRATION.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially diminished. Concomitantly, the level of fibrin(ogen) degradation products (FDP/fdp) is increased. The combination of reduced fibrinogen and increased FDP/fdp results in a prolongation of the thrombin time. While changes in any of these parameters may serve as confirmation of the existence of a lytic state, no adjustment of dosage should be made on the basis of these test results.

ADVERSE REACTIONS

Incidence and Management

Strict observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.

BLEEDING

Incidence

Where thrombolytic agents (streptokinase and urokinase) were used in the same controlled clinical trial, severe bleeding (patients receiving a transfusion of greater than two units of blood) was seen in 4 and 6%, respectively. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Less severe spontaneous bleeding has been observed during urokinase treatment at approximately twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of percutaneous trauma is frequent; hence, all invasive procedures, especially arterial punctures and intramuscular injections must be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding occurred in approximately one out of five patients treated with urokinase.

Management of Severe Bleeding

In case of serious bleeding, urokinase therapy must be discontinued. If blood loss has been large, packed red cells are indicated. Plasma volume expanders (other than Dextran) are indicated to replace blood volume deficit. If only whole blood is available, it may also be used. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, it may be considered if the hemorrhage is unresponsive to blood replacement. (See WARNINGS.)

ALLERGIC REACTIONS

Although urokinase is a protein of human origin, and *in vitro* tests with the drug, as well as intradermal test in humans, gave no evidence of induced antibody formation, the possibility of serious allergic reactions (including anaphylaxis) occurring with its use cannot be excluded. Relatively mild allergic reactions, e.g., bronchospasm and skin rash, were reported rarely.

FEVER

Febrile episodes occurred in approximately two to three out of 100 patients. A cause and effect relationship has not been established. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is recommended.

DOSAGE AND ADMINISTRATION

Dosing

ABBOKINASE IS INTENDED FOR INTRAVENOUS INFUSION ONLY.

A priming dose of 2,000 I.U./lb (4,400 I.U./kg) of ABBOKINASE is given as the Abbokinase-Normal Saline admixture over a period of ten minutes. This is followed by a continuous infusion of 2,000 I.U./lb/hr (4,400 I.U./kg/hr) of ABBOKINASE (given as the Abbokinase-Normal Saline admixture) for 12 hours. The total volume of fluid administered should not exceed 200 ml.

Administer ABBOKINASE (urokinase for injection) by means of a constant infusion pump that is capable of delivering a total volume of 195 ml.

Anticoagulation After Terminating Urokinase Treatment

At the end of urokinase therapy, treatment with heparin by continuous intravenous infusion is recommended. Heparin treatment should not begin until the thrombin time has decreased to ***less than twice*** the normal control value. See manufacturer's prescribing information for proper use of heparin.

of subsequent drug administration on the duration of this period. In the anterograde direction the magnitude of increase in the length of the effective refractory period of the accessory pathway after administration of procainamide, quinidine, ajmaline and amiodarone was related to its initial length. Only modest lengthening of this period could be accomplished in patients with an initially short period. Only amiodarone consistently caused moderate prolongation of this period. Patients with a short effective refractory period of the accessory pathway (at risk of high ventricular rates if atrial fibrillation supervenes and most in need of lengthening of this period) are least likely to benefit from commercially available drugs. Amiodarone might best protect such patients against life-threatening ventricular rates when atrial fibrillation supervenes.

670 Pharmacokinetic-Hemodynamic Studies of Nitroglycerin Ointment in Congestive Heart Failure

PAUL W. ARMSTRONG, JOYCE A. ARMSTRONG and GERALD S. MARKS with the technical assistance of JAMES McKINVEN and SUSAN SLAUGHTER

Documenting the bioavailability of nitroglycerin delivered percutaneously to patients with congestive heart failure, this study in 14 patients demonstrated a good correlation between the dose of nitroglycerin ointment and nitroglycerin bioavailability. Nitroglycerin ointment provided therapeutic levels of nitroglycerin associated with prompt substantial hemodynamic benefit as demonstrated by decreased pulmonary capillary wedge pressure and right atrial pressure 30 minutes after application in selected patients with heart failure. There was a greater decrease in the pulmonary capillary wedge pressure in the small dose group (31 percent) compared with the large dose group. A subset of patients was identified who had minimal response to nitroglycerin despite plasma concentrations of 9 ng/ml. Such lack of response probably represents target organ resistance in peripheral arterioles and veins, can be anticipated by prior intravenous nitroglycerin infusion and is best detected by hemodynamic monitoring.

677 Simultaneous Anterograde Fast-Slow Atrioventricular Nodal Pathway Conduction After Procainamide

JOSEPH ANTHONY C. GOMES, PRITPAL S. KANG, GEORGE KELEN, RAHMAN KHAN and NABIL EL-SHERIF

Electrophysiologic recordings in three patients with paroxysmal supraventricular tachycardia before and after the intravenous infusion of 500 mg of procainamide revealed that this drug altered conduction and refractoriness of the anterograde fast and slow pathways so that simultaneous conduction could occur during atrial pacing, producing a double ventricular response and a slow-fast echo or tachycardia, or both. The electrophysiologic data in all three indicated that the region of the atrioventricular (A-V) node was the site of reentry. The differential effects of procainamide on anterograde fast and retrograde fast pathways suggest that these are two functional A-V nodal fast pathways, one for anterograde and the other for retrograde conduction. The retrograde fast pathway is physiologically and perhaps anatomically distinct from the anterograde fast pathway. The drug response of the retrograde fast pathway resembles that of Purkinje muscle, whereas the response of the anterograde fast pathway resembles that of the A-V node.

REVIEWS

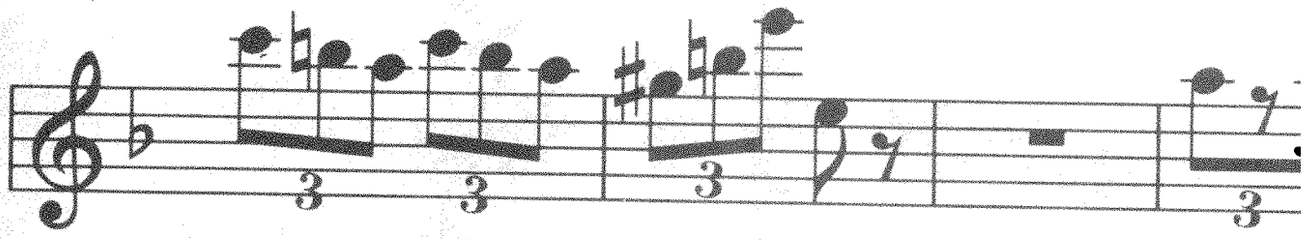
685 Systemic Arterial Hypertension Associated With Cardiac Surgery

FAWZY G. ESTAFANOUS and ROBERT C. TARAZI

Serious hypertension can occur with any type of cardiac surgery. It has been reported to complicate the course of 30 to 50 percent of patients subjected to coronary bypass surgery. The hypertensions have different causes and mechanisms. A classification such as the one proposed in this review, based on well defined clinical events such as timing in relation to surgery, allows an acceptable definition of hypertension that permits comparison of reports from different observers. Careful appraisal of antihypertensive therapy is an essential step in preparation for surgery. The definition of the mechanisms underlying the increase in arterial pressure at different stages of surgery or in the postoperative period facilitates a rational choice of therapy. Prophylactic, general and specific antihypertensive measures to control the more common type of hypertension complicating cardiac surgery are outlined.

continued on page A44

An impressive therapeutic performance...



In tune with contemporary antihypertensive thinking

Today antihypertensive therapy has gone beyond the empirical addition of one drug to another. Today's clinician looks for agents that coordinate their action for smoother, more effective control.

A prime example is increasing use of the Apresoline/beta-blocker/diuretic regimen in moderate-to-severe hypertension. Beta blockers, though effective and generally well tolerated, do not lower the high peripheral resistance found in virtually all long-standing hypertension. As a vasodilator, Apresoline deals directly with the problem. It can decrease total peripheral resistance by more than 60%.

Beta blockers, on the other hand, specifically reduce cardiac output, which tends to rise through reflex action with Apresoline therapy, while diuretics counteract the retention of sodium and extracellular fluid.

Harmonizing with the antihypertensive life-style

The Apresoline/beta-blocker/diuretic regimen is relatively free of serious side-effect problems that interfere with daily living.

As the only therapeutic action of Apresoline is its direct arteriolar vasodilator effect, it avoids many distressing side effects. Sexual dysfunction, drowsiness, lethargy, and sedation are virtually unknown. Postural hypotension is rare. These side effects are usually also avoided with a beta blocker.

Accompanying a fall in blood pressure from Apresoline is an increase in cardiac rate and output. Apresoline also maintains or increases renal and cerebral blood flow. As with any antihypertensive agent, use with caution in patients with advanced renal damage. Contraindicated in coronary artery disease.

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TABLETS

INDICATIONS

Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS

Hypersensitivity to hydralazine; coronary artery disease; and mitral valvular rheumatic heart disease.

WARNINGS

Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary.

Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is symptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms.

A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.

Use MAO inhibitors with caution in patients receiving hydralazine.

When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy

Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS

Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.

The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.

In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy.

Periodic blood counts are advised during prolonged therapy.

The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

Adverse reactions with Apresoline are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.

Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.

Less frequent: Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION

Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.

The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.

In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

665115 C80-15 (1/80)

Consult complete product literature before prescribing.

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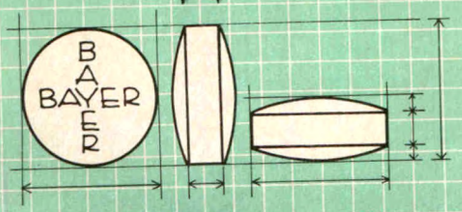
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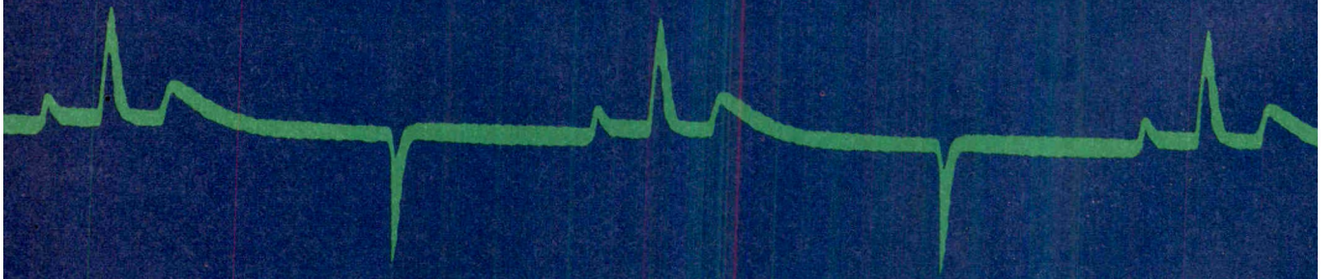
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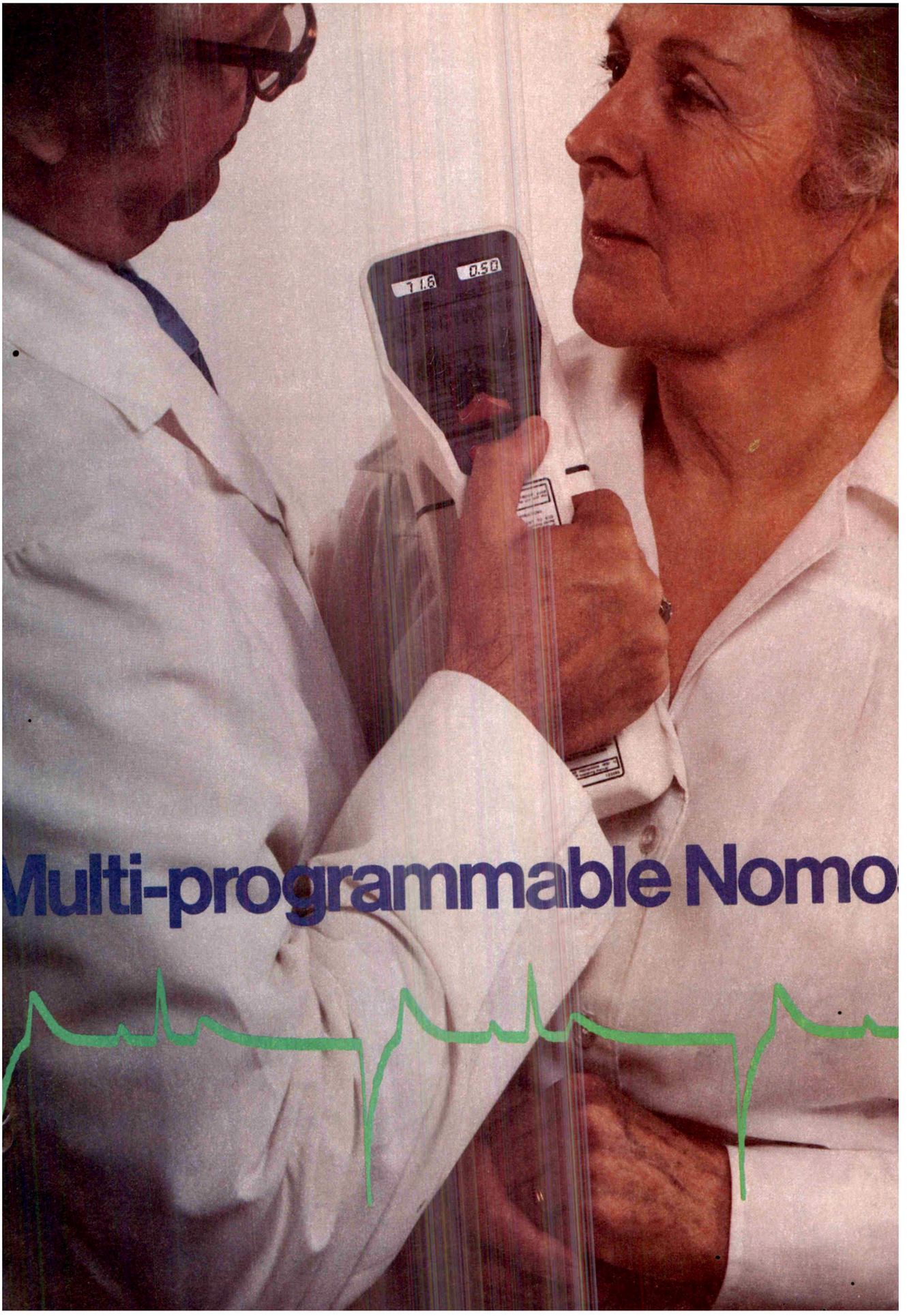
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CASE REPORTS

695 **Selection of Angina-Free Patients With Severe Left Ventricular Dysfunction for Myocardial Revascularization**

CARY W. AKINS, GERALD M. POHOST, ROMAN W. DeSANCTIS and PETER C. BLOCK

Stress thallium-201 myocardial imaging proved useful in two angina-free patients with severe congestive heart failure to identify clinically silent areas of ischemic myocardium and to distinguish between scar and reversibly ischemic myocardium as a cause for akinesia of left ventricular wall segments. Myocardial revascularization improved the patients' clinical state and findings in the postoperative nuclear scans. Because the sensitivity of angina as a clinical marker of severe coronary artery disease is probably very low, other clinical presentations of coronary artery disease, such as functional mitral insufficiency, atrial and ventricular arrhythmias, congestive heart failure and atypical pain and dyspnea, might be clinically grouped as ischemic equivalents of coronary artery disease.

SPECIAL DEPARTMENTS

701 **Letters to the Editor**

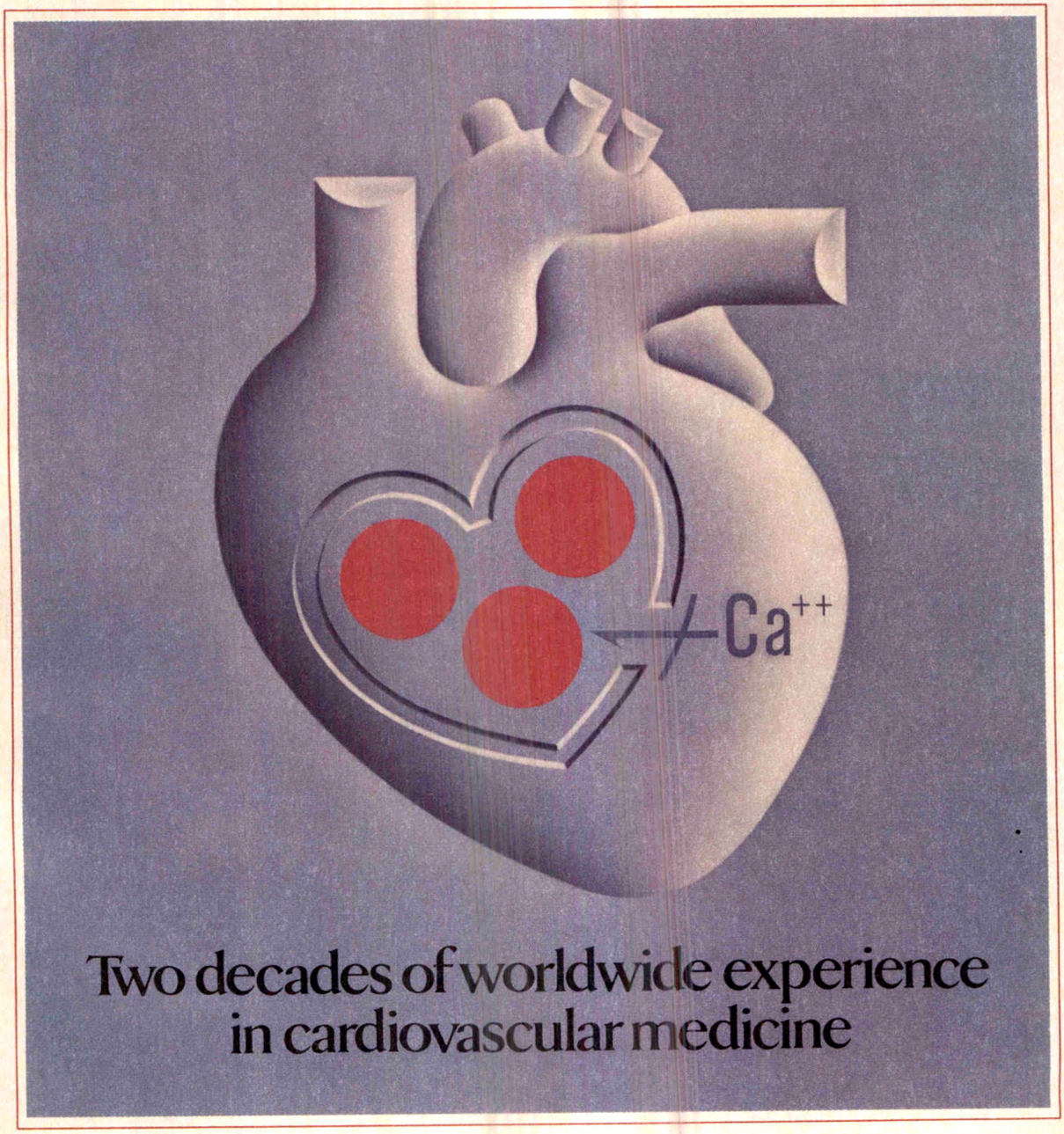
718 **American College of Cardiology News**

CORRECTION

The dose of quinidine was incorrectly given on page 1196 of the June issue of the Journal (Doherty JE, Straub KD, Murphy ML, de Soyza N, Bissett JK, Kane JJ. Digoxin-quinidine interaction. Changes in canine tissue concentration from steady state with quinidine. Am J Cardiol 1980;45:1196–200). On line 7, page 1196 of the Methods section, the dose of quinidine should be 80 (not 8) mg.

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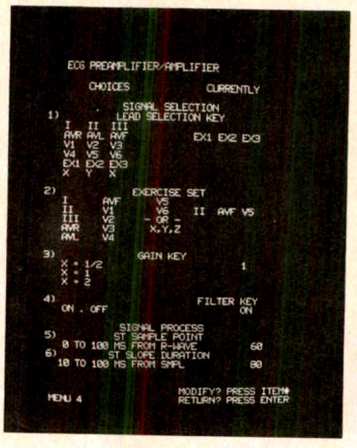
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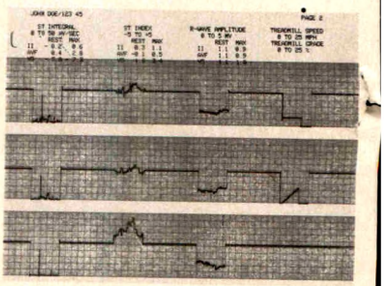
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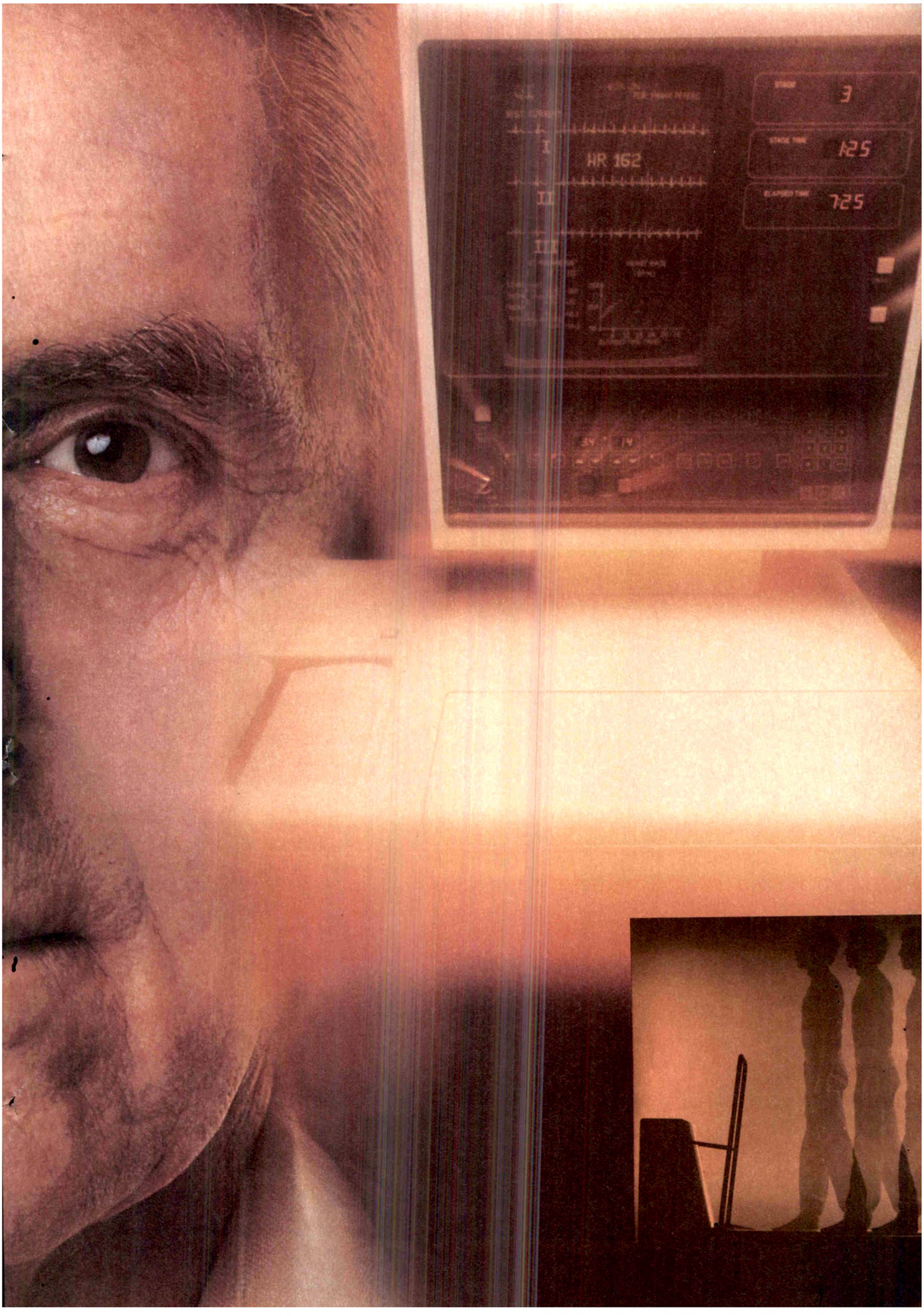
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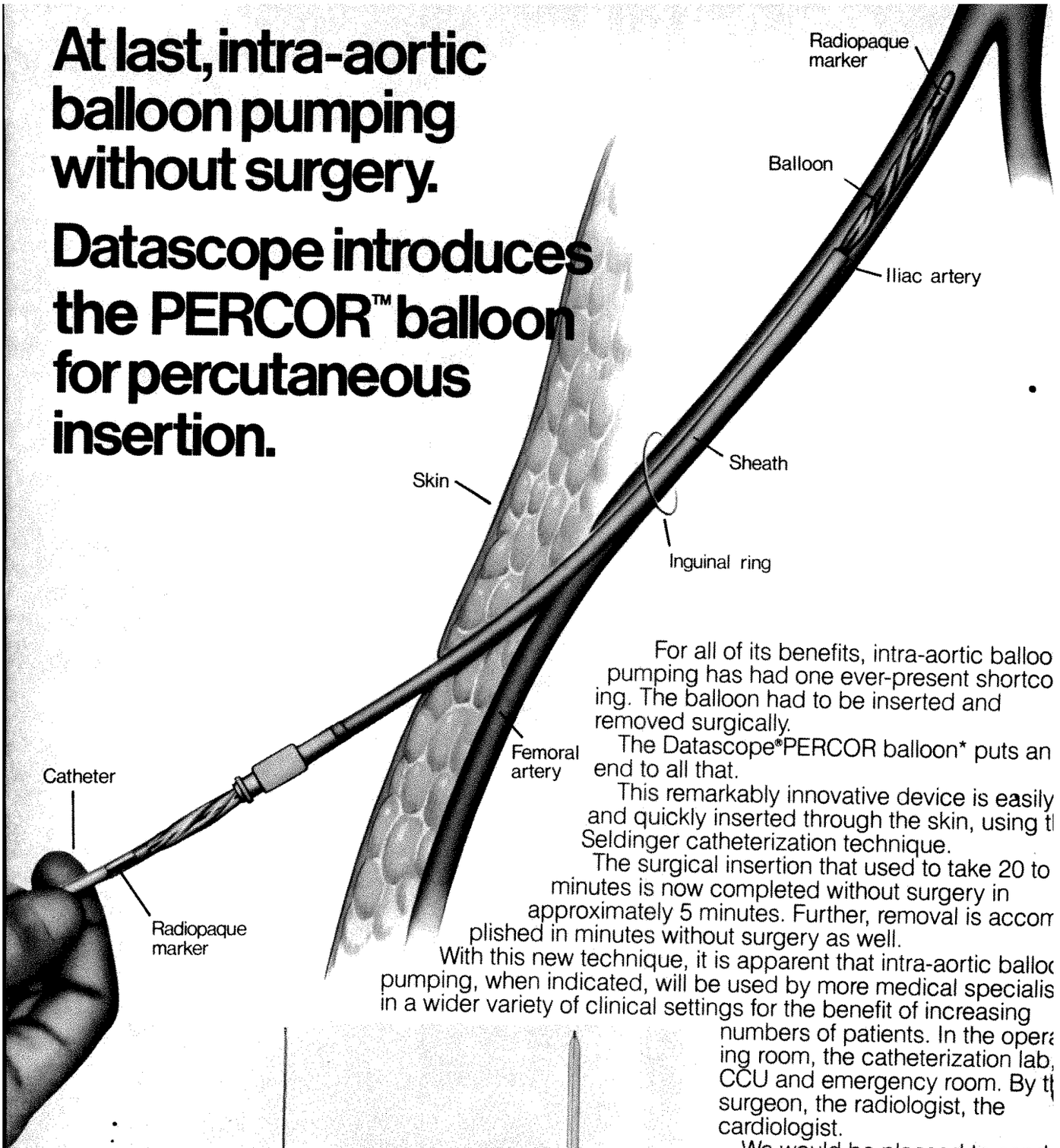
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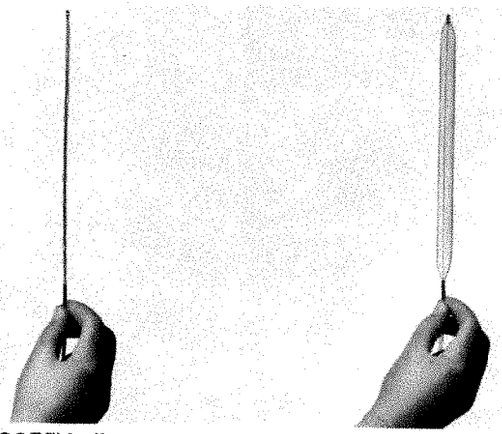
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Clinical reference: *Preliminary Clinical Experience With Percutaneous Intra-Aortic Balloon Pumping (IABP)*, V. A. Subramanian, Jonathan Goldstein, Thomas A. Sos, John C. McCabe, Eddie Hoover & William A. Gay, Jr., New York Hospital, New York, NY. Abstract published in CIRCULATION, Part II, Vol. 60, No. 4, October 1979, PP. II-103• *U.S. and foreign patents pending.

An open letter to our friends in the Medical Community.



We have looked forward, each year, to the Annual Meeting of The American Heart Association, because it is at these prestigious gatherings that we have had an opportunity to show our appreciation for the support the Medical Community has shown to our company and our products. We have done this by hosting entertainment receptions, especially designed for convention attendees. Perhaps you have been our guest.

The reaction we've had has always been favorable, so it came as quite a surprise when we received a notice from the AHA this year that (it) "has ruled that industry sponsored mass entertainment activities are prohibited..." during the convention dates.

Ruled? The AHA has *ruled* that we, and other companies, cannot host functions for our friends in the profession? Well, you can imagine how startled we were to hear *that!*

Help us to understand such a "ruling." Is it reflective of *your* views? Take a moment now to fill out the simple questionnaire below and send it back to us, so that we can know of your feelings on the subject.

We wish to play by the rules, of course. But what should we do when such "rules" infringe upon the rights of a company to say "thank you" to the people we've been priviliged to work with over the year?

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Do you recommend that Pacesetter hold a Las Vegas/Casino Night Party at the AHA meeting in November?	☐	☐
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COMMENTS: _____

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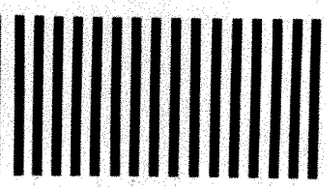
(Your name is optional, of course. But please do send us your feelings. Thanks.)

Let us hear from you.

On the other side of this sheet is a questionnaire on the subject of company-sponsored entertainment and/or receptions at Medical conventions. Please take a moment to read it, and let us have your thoughts. A complete tabulation of the results of this survey will be made available.

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The Human Cardiovascular System
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By: J. T. Shepherd and P. M. Vanhoutte

This textbook is designed for use in medical school courses in introductory cardiology and physiology, as well as for more advanced use by those beginning specialty training or others wishing a general review of the basic function of the human cardiovascular system. Beginning with a discussion of the normal functioning of the cardiovascular system, the text logically leads into discussions of common pathological situations and their management.
375 pp., $14.95 (paper), $25.00 (cloth) (1979) ISBN 0-89004-367-1

Pharmacology of Antihypertensive Drugs

Editor: A Scriabine

Each chapter in this volume has been prepared by pharmacologists and other medical specialists who actively participated in the development of antihypertensive drugs and were in many cases the actual discovers and developers of the activity of the drug they describe. For each antihypertensive drug in current use or advanced development, chapters review mechanisms of action, secondary pharmacological properties, and side effects.
472 pp., $37.50 (1980) ISBN 0-89004-329-9

Prostacyclin

Editors: J. R. Vane and S. Bergström

This volume reviews in comprehensive fashion our current understanding of the chemistry, physiology, and pharmacology of prostacyclin and its analogs, and discusses their therapeutic potential. Much of the volume focuses on the interaction between the effects of prostacyclin and thromboxane A_2. The balance between these two members of the prostaglandin family has tremendous significance for the state of health or disease within the cardiovascular system.
472 pp., $43.00 (1979) ISBN 0-89004-330-2

The Aging Heart: Its Function and Response to Stress
(Aging, Vol. 12)

Editor: M. L. Weisfeldt

This volume discusses the pathophysiological changes that occur in the human cardiovascular system as a function of age. Sections focus on the contractile and elastic properties of cardiac muscle, the heart as a single organ within the body, the integration of the components of the cardiovascular system, and its response to pharmacologic agents.
335 pp., $29.50 (1980) ISBN 0-89004-307-8

Mechanisms of Cardiac Morphogenesis and Teratogenesis
(Perspectives in Cardiovascular Research, Vol. 5)

Editor: T. Pexieder

This volume presents a multidisciplinary analysis of the cellular and subcellular mechanisms regulating cardiac morphogenesis and teratogenesis in the embryo. The material is organized into three major areas: organogenesis of the heart, cellular and subcellular mechanisms, and regulatory aspects. Each section includes findings from both human and animal studies, particularly on the rat and chick embryo.
Approximately 525 pp., 251 figures, tentatively $48.00
(October 1980) ISBN 0-89004-460-0

Journal of Cardiovascular Pharmacology

Editors-in-Chief: Leon I. Goldberg and Jan Koch-Weser

This bimonthly journal aims to bring together new information about cardiovascular drugs from research workers and the clinicians who use these drugs in therapy. Its scope covers all old and new pharmacologic agents that directly or indirectly affect the heart and blood vessels and their contents. The journal publishes original or review articles on the creation of such drugs and on their mechanism of action, development and evaluation, therapeutic effectiveness, metabolism, side effects, and interactions.
Personal subscriptions, U.S. $48.00; elsewhere $59.00
Institutional subscriptions, U.S. $58.00; elsewhere $68.00

Prostaglandins and Cardiovascular Disease
(Atherosclerosis Reviews, Vol. 8)

Editor: R. J. Hegyeli

This volume reviews our current understanding of the role of prostaglandins in the normal functioning of the cardiovascular system, in a variety of pathologic conditions, and in medical management of these conditions. Topics include the role of prostaglandins in the control of blood pressure, platelet aggregation, and cyclic AMP levels in heart muscle and arterial walls. The potential use of prostaglandins and their derivatives as pharmacologic agents is also considered, as well as the mechanisms of action of drugs such as antianginal and antihypertensive agents that require the presence of prostaglandins.
Approximately 200 pp., tentatively $25.00 (October 1980)
ISBN 0-89004-516-X

Measurement and Control of Cardiovascular Risk Factors
(Atherosclerosis Reviews, Vol. 7)

Editor: R. J. Hegyeli

This volume focuses on the control of cardiovascular disease by environmental modification. Chapters discuss the epidemiology of coronary artery disease, the major predisposing factors, the role of smoking and diet in its development, drug treatment of primary hyperlipidemias, and the role of vasospasm and other modulatory factors. This volume will be of interest to all those concerned with the development and management of coronary artery disease, including specialists in cardiology and internal medicine and clinical researchers in this field.
340 pp., $34.00 (1980) ISBN 0-89004-396-5

Nutrition, Lipids, and Coronary Heart Disease, A Global View
(Nutrition in Health and Disease, Vol. 1)

Editors: R. Levy, B. Rifkind, B. Dennis, and N. Ernst

"A lucid, well integrated, well documented discussion of the complex relation between diet and coronary-artery disease. Seldom has the topic received such careful scrutiny and balanced, succinct treatment as in this book."– New England Journal of Medicine
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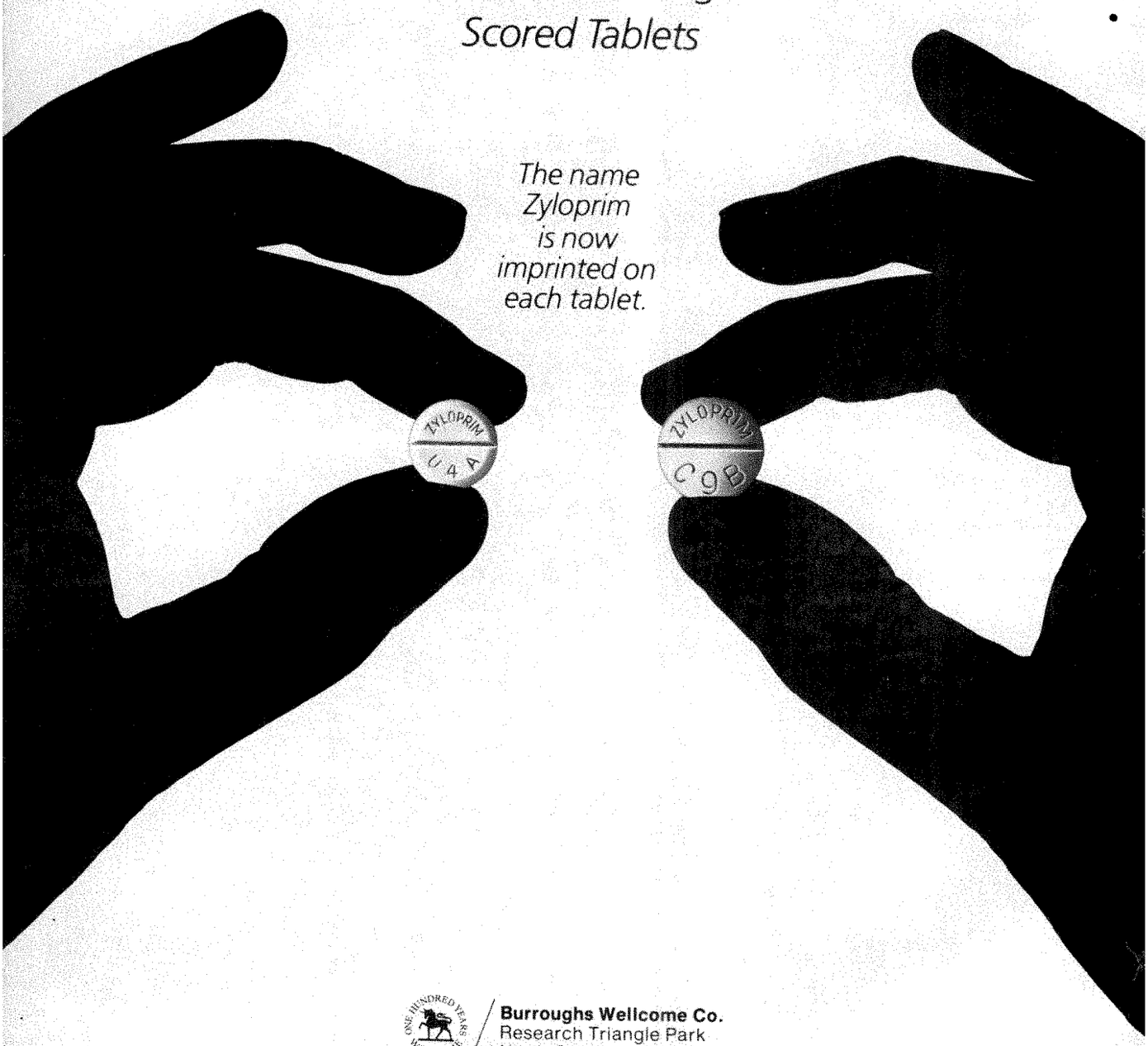
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CLINICAL STUDIES

Absence of Correlation Between Coronary Arterial Atherosclerosis and Severity or Duration of Diabetes Mellitus of Adult Onset

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The relation between the severity and duration of diabetes mellitus and the severity of ischemic heart disease is uncertain. The clinical findings and the findings at autopsy were studied in 185 patients with diabetes mellitus of adult onset who ranged in age from 37 to 91 years and had a clinical diagnosis of diabetes established for a few days to 50 years before death. No statistically significant association was demonstrated either by simple correlation or by multivariate regression analysis between the clinically diagnosed severity or duration of diabetes and either the overall coronary disease, the number of diseased vessels or the number of myocardial infarctions. The presence of other expected correlations in the multivariate analysis suggested that the results of this study were not spurious. However, comparison with 185 age- and sex-matched control patients revealed that *on the average,* diabetic patients have more overall coronary disease ($p < 0.002$), more diffuseness of coronary disease ($p < 0.005$), more coronary collateralization ($p < 0.001$), more vessels involved by atherosclerosis ($p < 0.001$) and more myocardial infarcts ($p < 0.001$). The results suggest that although diabetes mellitus of adult onset is a condition in which the larger coronary arteries are subject to more atherosclerosis than are those in nondiabetic subjects, the progression of the atherosclerotic disease is unrelated to the duration or severity of the diabetes mellitus.

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Although coronary artery disease may not be an inevitable consequence of diabetes mellitus,[1–4] patients with diabetes of adult onset appear to have more coronary artery disease than do control populations not suffering from diabetes.[5–16] Previous studies have indicated that patients with adult onset diabetes have increased atherosclerosis,[8,17–19] myocardial infarction[16,20,21] and morbidity and mortality from cardiovascular disease.[10,22–25] Whereas microvascular changes are the hallmark of renal and retinal tissue in diabetes,[16] it is not known whether cardiac injury results from large vessel coronary disease,[27,28] microangiopathy[29,30] or an interstitial myocardial process.[31–34]

Recent studies using coronary angiography in evaluating patients for surgical correction of atherosclerotic heart disease have led to contro-

versy concerning whether the angiographic findings in diabetic patients with vascular disease are different in type and severity from those of others so evaluated.[28,29,34–41] In addition, most clinical studies have understandably examined only those patients seeking medical help for symptoms related to vascular disease. Therefore, substantial information on asymptomatic diabetic patients or those refusing invasive clinical techniques is lacking, a point of considerable importance when considering the increased incidence of painless myocardial infarction among diabetic patients.[6,42–45]

We reviewed the clinical and pathologic data on 185 consecutive autopsy patients with diabetes of adult onset, and examined their postmortem coronary arteriograms in an effort to see whether correlations existed between the clinically determined severity of diabetes and the extent of coronary artery disease. We also compared the arteriograms of diabetic patients with those of age- and sex-matched nondiabetic patients coming to autopsy during the same period. Our findings indicate that, regardless of the cause of death, diabetic patients as a group have more angiographically determined coronary disease than a control population coming to autopsy. However, neither the clinically evaluated degree of diabetes nor its duration was associated with the extent or severity of angiographically evident coronary artery disease.

Methods

Study patients: One hundred eighty-five patients were included in this study. All had a clinically established diagnosis of diabetes mellitus of adult onset, underwent autopsy at The Johns Hopkins Hospital between 1968 and 1978 and had had a heart study performed with a standard method using coronary arteriography and fixation in distension.[46] The patients ranged in age from 37 to 91 years (average 65); 100 were men (57 white and 43 black) and 85 were women (35 white and 50 black). Hearts studied in this manner comprised 22 percent of patients undergoing autopsy at The Johns Hopkins Hospital during this period, and were, in general, selected on the basis of expectation of cardiac disease irrespective of the presence of diabetes mellitus. The major interest in performing this procedure was the evaluation of ischemic heart disease, so the heart in such patients was usually studied and consequently coronary artery disease was disproportionately represented in the series of injected hearts. The heart was studied in most adult patients with previous cardiac surgery, irrespective of type; in contrast, almost no infants or children were included in the series of cases examined.

Preparation of the heart: Coronary arteries were injected at a pressure of 100 to 150 mm Hg with a barium-pigment-gelatin mass to which formalin had been added. After injection, cannulas were tied into the atria and great vessels, the remaining orifices were ligated and the chambers were distended with 10 percent formalin through the cannulas at 30 to 40 mm water pressure while the heart was suspended in a container of formalin. After overnight fixation, photographs and stereoscopic radiographs were prepared of the fixed distended heart and of the transverse sections into which it was sliced. The coronary arteries were transected at 2 to 3 mm intervals and compared with the radiographic findings. Representative portions of myocardium, including all grossly discernible lesions, and portions of the coronary arteries were taken for histologic examination.

Assessment of severity of diabetes: The medical records of all patients were reviewed to assess the clinical severity of diabetes, including associated cardiovascular, retinal, renal and neurologic disease. The age at which diabetes was first diagnosed, age at death, race and sex were noted. Juvenile diabetic patients (age less than 17 years at the time of diagnosis) were excluded. The duration between the clinical diagnosis of diabetes and death ranged from a few days to 50 years (average 9.5 years). The severity of diabetes was graded as *trivial* in 47 patients, *mild* in 81, *moderate* in 33 and *severe* in 19. Five patients had insufficient clinical data to categorize the severity.

Values for serum glucose, serum creatinine, serum urea nitrogen, serum cholesterol and hematocrit were recorded. Many clinical and autopsy findings were best assessed with a subjective grading system. We used a scale of *none, slight, low moderate, high moderate and severe* for each such feature, and normalized these grades on a scale of 0 to 100 to make the regression coefficients comparable with one another. We assessed the severity of diabetes in each patient on the basis of objective data and the clinicians' impressions as stated in the medical record: *slight* for maintenance of normal serum glucose levels without therapy or with dietary restrictions only; *low moderate* for therapy with oral hypoglycemic agents without manifestations of diabetes-related vascular, retinal, renal or neurologic disease; *high moderate* for oral hypoglycemic therapy with known vascular, retinal, renal or neurologic disease or use of insulin, or both; and *severe* for insulin-dependency with a history of either episodes of acidosis, severe retinopathy or peripheral vascular disease. The type and duration of therapy, including control by diet, oral hypoglycemic agents or insulin, were recorded: *none* for no therapy, *moderate* for continuous or sporadic application of therapy for less than 2 years and *severe* for application of therapy for 2 or more years. The number of episodes of acidosis and coma was recorded.

Retinopathy was graded as *slight* for general constriction of the retinal vessels; *low moderate* for the presence of retinal hemorrhages or microaneurysms, or both; *high moderate* for soft or hard exudates; and *severe* for retinitis proliferans or blindness. Urinalysis performed within 1 month of death was graded as *none* for detectable glucose, protein or ketone bodies in the urine; *slight* for recurrent low grade glycosuria; *low moderate* for recurrent low grade proteinuria (at least 1+ protein by standard reagent strip) with or without glycosuria; *high moderate* for recurrent high proteinuria with glycosuria; and *severe* for recurrent proteinuria or glycosuria with detection of ketones. Renal failure was graded as *none* for no clinically discernible disease; *slight* for recurrent proteinuria, abnormally elevated serum creatinine and abnormally elevated blood urea nitrogen; *low moderate* for episodes of renal failure; *high moderate* for chronic renal failure; and *severe* for renal failure requiring dialysis.

Grading of hypertension and cardiovascular disease: Hypertension was graded as *absent* for normotensive subjects; slight for arterial pressure less than 150/95 mm Hg; *low moderate* for arterial pressure greater than 150/95 mm Hg with a history of antihypertensive therapy; *high moderate* for arterial pressure greater than 160/110 mm Hg with a history of antihypertensive therapy; and *severe* for arterial pressure greater than 200/140 mm Hg. The number of cerebral vascular accidents was recorded.

Peripheral vascular disease in a lower limb was graded as *slight* for trophic skin ulceration, *low moderate* for intermittent claudication, *high moderate* for toe amputation and

severe for more proximal amputations or gangrene. Peripheral neuropathy was graded to reflect the extent of primarily sensory impairment in limbs, including absent ankle jerks, loss of vibration sense and numbness and tingling. Amputations were graded in terms of the amount of limb lost.

Angina, if present, was graded as *slight* for at least one recorded complaint of chest pain before the final hospital admission, *moderate* for repeated episodes and *severe* for incapacitation. Congestive heart failure was graded as *absent* for patients without failure, *slight* if well controlled with or without medication, *moderate* for recurrent failure requiring medication and hospitalization and *severe* for refractory failure. In addition, electrocardiographic abnormalities by history were graded as *absent* for no abnormalities in the final or previous hospital admission, *moderate* for such nonspecific changes as ST-T wave changes and *severe* for at least one episode of abnormal readings in a recent admission. The patient's obesity, number of pack-years of cigarette smoking and family history of diabetes were recorded.

Autopsy data: We collected autopsy data including weight of the heart, liver and kidneys, and the degree of atherosclerosis involving the coronary, pulmonary, cerebral and systemic circulations. The thickness of the abdominal panniculus was taken as a measure of obesity. Vascular disease was graded as *none* for no intimal disease, *mild* for an occasional atherosclerotic plaque, *moderate* for multiple plaques and *severe* for atherosclerosis with partial or total arterial occlusions. The number of myocardial infarcts ascertained during postmortem study was recorded.

Grading of coronary artery disease: The postmortem arteriograms were evaluated for the number of the three major vessels (left anterior descending, left circumflex and right coronary arteries) with significant (greater than 75 percent) reduction of the luminal area. The overall severity of atherosclerosis demonstrated angiographically, confirmed by serial transections at 2 to 3 mm intervals of the epicardial coronary arteries, was graded as *none* for no discernible disease, *slight* for small focal irregularities, *low moderate* for occasional (less than 75 percent) obstructions at several points or one significant lesion, *high moderate* for one vessel occlusion or numerous lesions and *severe* for two or more significant or occlusive lesions. The grade of diffuseness of atherosclerosis was assessed on the basis of the number and confluence of atheromas. Tortuosity of the epicardial coronary arteries[47] was graded as *slight,* when only gentle waviness of the vascular course was seen, to *severe* when arteries formed loops and hairpin curves in their course. The degree of development of coronary arterial collateral connections was assessed on the basis of their size and tortuosity.[48] A diameter (D_{Th}) for a theoretic single coronary artery supplying blood to the heart[47,49] was calculated from measurements of the diameters of the major left and right coronary arteries by the formula: $(D_{Th})^3 = (D_{Right})^3 + (D_{Left})^3$.

Histology: We reviewed representative histologic sections of hematoxylin-eosin–stained heart, pancreas and kidney tissue, without knowledge of the clinical history. Interstitial vacuolar change in the myocardium and intimal disease of intramyocardial coronary arteries were graded. We made an overall assessment of renal glomerular disease as well as of specific renal disease such as diffuse and nodular intercapillary glomerulosclerosis and intrarenal fibroelastosis. Random sections of pancreatic tissue were evaluated for hyalinization of the islets, hyperplasia of the islets and interstitial fat. Grading of pathologic variables represented the consensus of two observers, and was made without knowledge of the clinical features of the patient.

Analysis of data: Correlation coefficients (Pearson's r) were calculated and examined for all pairs of the 54 variables. These findings were used in part as the basis for deciding which variables would be of interest in subsequent analyses. Forward and backward stepwise multivariate regression analyses were then performed using each of 26 features (indicated by an asterisk in Table I) as the dependent variable or variable to be predicted.[50,51] In the forward regression, variables were added singly until no further variables achieved a 0.01 level of significance with the dependent variable. The 0.01 level of significance was selected because of the high likelihood of spurious results with more permissive significance levels when so many variables (that is, 26) were being evaluated.

TABLE I

Variables Examined After Initial Screening

Clinical Findings	Pathologic Findings
Age*	Panniculus thickness*
Severity of diabetes*	Heart weight*
Duration of diabetes*	Overall coronary arterial atherosclerosis*
Dietary therapy	Number of diseased coronary arteries
Oral hypoglycemic agent therapy	Diffuseness of coronary atherosclerosis
Insulin therapy	Coronary arterial collaterals
Episodes of acidosis*	Epicardial coronary arterial tortuosity*
Episodes of coma*	Diameter of theoretical coronary artery
Retinopathy*	Intramyocardial arterial disease*
Urinalysis	Vacuolar change of myocardium
Renal failure*	Number of myocardial infarcts*
Hypertension*	Kidney weight*
Cerebrovascular accidents*	Intrarenal intimal fibroelastosis*
Peripheral vascular disease*	Overall glomerular disease*
Peripheral neuropathy*	Nodular intercapillary glomerulosclerosis
Amputations*	Diffuse intercapillary glomerulosclerosis
Angina*	Liver weight*
Congestive heart failure*	Hyalinization of pancreatic islets*
	Hyperplasia of pancreatic islets*
	Pancreatic interstitial fat
	Generalized atherosclerosis
	Cerebral atherosclerosis
	Pulmonary atherosclerosis

* Variables used in multivariate regression analysis.



FIGURE 1. Postmortem coronary arteriograms from patients with diabetes mellitus. **Left,** the heart of a 48 year old man with a 13 year history of diabetes mellitus requiring insulin therapy and complicated by peripheral neuropathy and retinopathy that had progressed to blindness. There is virtually no coronary arterial atherosclerosis. **Right,** the heart of a 67 year old woman with a 7 year history of diabetes mellitus treated with oral agents and complicated by leg amputation, cerebral infarcts and ischemic heart disease. The coronary atherosclerosis is extremely severe with significant obstructions or occlusions of several major arteries.

Control patients: Age- and sex-matched control nondiabetic patients whose heart had also been studied at autopsy after postmortem coronary arteriography and fixation in distension were selected. These patients were evaluated as described previously for body and organ weights, pathologically identified myocardial infarcts and the various semiquantitative estimates made from the postmortem coronary arteriograms. The data from these patients were compared with the Student's t test with data from the corresponding diabetic patients.

Results

Severity of diabetes versus severity of coronary disease: Among the 54 variables studied in the 185 patients with diabetes mellitus of adult onset, several were excluded from further assessment because data were (1) frequently not available (serum creatinine, urea nitrogen and cholesterol, pack-years of smoking and family history of diabetes), (2) deemed inconclusive (hematocrit, electrocardiographic changes, weight and height), (3) not further analyzed (race and sex), or (4) found redundant after pairwise correlation (obesity replaced by panniculus thickness, and age at onset of diabetes replaced by duration of disease). The remaining 41 variables (Table I) were examined. Significant correlations with postmortem coronary arteriographic findings (Fig. 1) are noted in Table II. Despite positive correlations between coronary artery disease and both clinically determined angina and autopsy-documented myocardial infarction, there was no significant association between overall coronary arterial atherosclerosis and either the duration or the severity of diabetes mellitus.

TABLE II

Simple Correlation Coefficients for all Among 40 Variables That Significantly ($p < 0.05$) Correlated With Overall Coronary Arterial Atherosclerosis

Variable	Pearson's r	Degrees of Freedom
Renal failure	−0.22*	181
Angina	+0.41†	183
Number of diseased coronary arteries	+0.89†	183
Diffuseness of coronary atherosclerosis	+0.81†	183
Coronary arterial collateral vessels	+0.80†	178
Epicardial coronary arterial tortuosity	−0.36†	182
Diameter of theoretic coronary artery	−0.49†	155
Vacuolar change of myocardium	+0.42†	176
Number of myocardial infarcts	+0.64†	180
Generalized atherosclerosis	+0.41†	182

* $p < 0.01$; † $p < 0.001$.

Histopathologic change versus clinical diabetes: The histopathologic changes in the heart, kidney and pancreas (Fig. 2) that had significant correlations with clinically determined diabetes are given in Table III. Hyalinization of the pancreatic islets was significantly correlated with duration of diabetes ($p < 0.05$), whereas hyperplasia of the islets correlated with severity of diabetes ($p < 0.01$). Intrarenal intimal fibroelastosis correlated with the severity of diabetes ($p < 0.01$) and the duration of disease ($p < 0.001$). Both diffuse and nodular intercapillary glomerulosclerosis showed significant correlation with the severity of diabetes and duration of disease. Intramyocardial arterial disease was correlated with the duration of diabetes ($p < 0.05$). Vacuolar change of myocardium had no correlation with the diabetic state, but did correlate with severity of coronary arterial atherosclerosis and ischemic myocardial injury. There were no significant correlations between severity of diabetes and either systemic, pulmonary or cerebral atherosclerosis. When patients were separated into three groups—those receiving no therapy or dietary treatment only, those receiving oral hypoglycemic

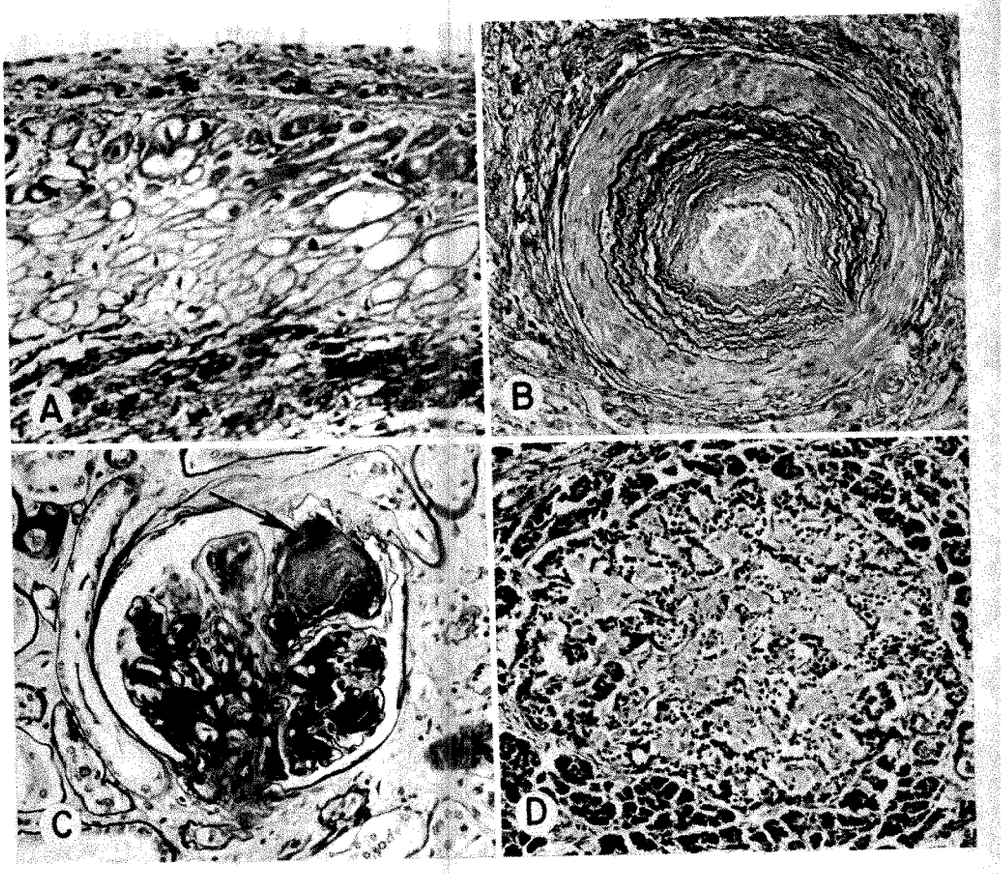


FIGURE 2. Histologic sections. **A,** subendocardial vacuolar change of myocardium. (hematoxylin-eosin, ×250, reduced by 26 percent.) **B,** intrarenal intimal fibroelastosis of an artery. (Verhoeff-van Gieson elastic stain, ×185, reduced by 26 percent.) **C,** a glomerulus showing nodular (**arrow**) and diffuse intercapillary glomerulosclerosis. (periodic acid-Schiff, ×350, reduced by 26 percent.) **D,** pancreatic islet of Langerhans with hyalinization. (hematoxylin-eosin, ×185, reduced by 26 percent.)

agents, and those receiving insulin—we found no significant differences among the coronary arterial atherosclerotic variables.

The results of the 26 starred variables in Table I that were entered in the forward multivariate regression are listed in Table IV.[50,51] Angina correlated positively with coronary artery disease and negatively with cerebrovascular accidents. Overall coronary arterial atherosclerosis correlated positively with the number of myocardial infarcts and angina but negatively with congestive heart failure and tortuosity. There were no significant correlations between severity of diabetes and coronary arterial atherosclerosis.

Control group findings: The age- and sex-matched control group (Table V) demonstrated significantly lower overall coronary arterial atherosclerosis ($p < 0.002$) than did the diabetic patients. In addition, the number of myocardial infarcts ($p < 0.001$), number of diseased coronary arteries ($p < 0.001$), diffuseness of coronary atherosclerosis ($p < 0.005$) and presence of coronary arterial collateral channels ($p < 0.001$) were significantly different from findings in diabetic patients.

Discussion

Influence of diabetes on severity of coronary artery disease: We were surprised to find that there was no correlation between the severity or duration of diabetes mellitus of adult onset and the severity of coronary arterial atherosclerosis in the patients studied. However, comparison of these patients to an age- and sex-matched control group showed that the diabetic patients did indeed have more coronary atherosclerosis, a finding in accord with previous data.[1,5–16] Although we found no significant differences in either heart weight or the tortuosity of the coronary vessels between the two groups, the diabetic patients showed an increase

TABLE III

Pathologic Changes Significantly Correlated ($p < 0.05$) With Severity and Duration of Diabetes

Variable	Pearson's r	Degrees of Freedom
Severity of diabetes with:		
Intrarenal intimal fibroelastosis	+0.24†	170
Overall glomerular disease	+0.36‡	170
Nodular intercapillary glomerulosclerosis	+0.37‡	170
Diffuse intercapillary glomerulosclerosis	+0.32‡	170
Hyperplasia of pancreatic islets	+0.20†	166
Duration of diabetes with:		
Intramyocardial arterial disease	+0.15*	171
Intrarenal intimal fibroelastosis	+0.24‡	170
Overall glomerular disease	+0.27‡	170
Nodular intercapillary glomerulosclerosis	+0.30‡	170
Diffuse intercapillary glomerulosclerosis	+0.25‡	170
Hyalinization of pancreatic islets	+0.15*	166

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; by Student's *t* test.

TABLE IV

Forward Multivariate Regression Analysis Predicting Selected Variables*

Retinopathy	= 2.44 + 0.22 renal failure + 0.27 overall glomerular disease + 0.25 severity of diabetes
Renal failure	= 5.92 + 0.32 overall glomerular disease + 0.36 congestive heart failure + 0.26 retinopathy − 6.04 number of myocardial infarcts
Hypertension	= 15.70 + 0.38 overall glomerular disease + 8.49 cerebral vascular accident
Angina	= 6.77 + 0.45 overall coronary arterial atherosclerosis − 13.32 cerebral vascular accident
Congestive heart failure	= −2.65 + 0.32 renal failure + 0.08 heart weight − 0.50 panniculus thickness
Heart weight	= 303.58 + 1.50 congestive heart failure + 2.33 kidney weight + 2.63 intramyocardial arterial disease
Overall coronary arterial atherosclerosis	= 57.15 + 12.51 number of myocardial infarcts − 0.22 congestive heart failure + 0.18 angina − 0.35 epicardial coronary arterial tortuosity
Epicardial coronary arterial tortuosity	= 86.39 − 0.16 overall coronary arterial atherosclerosis − 0.21 kidney weight − 0.02 heart weight
Intrarenal intimal fibroelastosis	= 28.88 + 0.25 overall glomerular disease + 0.24 age + 0.08 hypertension

* Independent variables (* in Table I) enter at a significance level of $p < 0.01$. Thirty-four patients were excluded because of insufficient data.

in angiographically determined numbers of diseased coronary vessels, diffuseness of coronary disease and collateralization of coronary arteries. In contrast, in a previous coronary angiographic study[38] of 35 diabetic and 35 nondiabetic patients, there were no differences between the two groups in mean luminal diameters of coronary arteries. Although Hamby et al.[29] evaluated patients with angina and found the extent of coronary artery disease reflected in both the number of vessels involved and the total coronary score to be the same for diabetic and nondiabetic patients, Dortimer et al.[34] found that adult diabetic patients with chest pain had more coronary artery disease but no more diffuse or inoperable disease. Our study, which reports the angiographic findings of both symptomatic and asymptomatic diabetic patients regardless of cause of death and clinical course, supports the studies that have indicated more coronary disease in this population.

TABLE V

Comparison of Coronary Artery Disease in 185 Diabetic Patients and 185 Age- and Sex-Matched Control Patients

Variable	Diabetic Patients*	Control Patients*	p†
Overall coronary arterial atherosclerosis	49.9 ± 29.7	39.7 ± 31.5	<0.002
Number of diseased coronary arteries	1.4 ± 1.2	1.0 ± 1.2	<0.001
Diffuseness of coronary atherosclerosis	41.6 ± 29.1	32.8 ± 29.8	<0.005
Coronary arterial collaterals	32.1 ± 32.1	20.7 ± 31.7	<0.001
Epicardial coronary arterial tortuosity	52.8 ± 17.3	55.5 ± 16.3	<0.1
Number of myocardial infarcts	1.2 ± 1.2	0.8 ± 0.9	<0.001

* Mean ± standard deviation; † Student's *t* test.

Lack of influence of duration and severity of diabetes: On the other hand, this group of diabetic patients by itself failed to show significant correlations between coronary arterial atherosclerosis and the duration or severity of diabetes. Significant associations between clinically determined diabetes and diabetic changes in the kidney, pancreas and the intima of intramyocardial vessels indicated that the severity of disease was indeed manifested in our patients in the form of pathologic tissue changes well recognized as being attributable to diabetes.[52] Prediction of selected variables by multivariate regression analysis (Table IV)[50,51] showed, at the significance level chosen, that severity of diabetes mellitus predicted only retinopathy. Retinopathy in turn entered into the prediction of renal failure, which was also dependent on glomerular disease and congestive heart failure. Angina pectoris was associated with severity of coronary atherosclerosis, but congestive heart failure was a function of renal failure and heart weight. Peculiar negative associations, such as that between angina and cerebrovascular accident and that between overall coronary arterial atherosclerosis and congestive heart failure, may simply reflect the fact that patients who came to autopsy with one condition had not yet experienced the other. Epicardial coronary arterial tortuosity, which is most marked in elderly patients with a small heart,[47] showed the expected associations, although its relation to kidney

weight is not understood. Another predicted association system is provided by intrarenal intimal fibroelastosis, which showed the expected dependence on glomerular disease, age and hypertension.

Clinical implications: Although our diabetic patients had an increased incidence of atherosclerosis their coronary angiograms did not reflect an angiographically evident progressive cardiac vascular disease. Neither the severity nor the duration of diabetes as determined clinically and substantiated by histopathologic changes in the kidney and pancreas was reflected in the severity of large vessel coronary disease. Although subtle changes in the interstitium[31–33] or small vessels of the heart[29,30] may represent cardiac analogs to diabetic retinal and kidney disease, causing the functional abnormalities of the heart as documented by some investigators,[31,40] the duration and severity of diabetes is not seen as determining the severity of angiographically discernible coronary disease. Our results suggest that the progress of large vessel coronary atherosclerotic disease in diabetes mellitus of adult onset takes place independently of the progress of the diabetes itself.

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Clinical and Arteriographic Variables Predictive of Survival in Coronary Artery Disease

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Survival, subsequent myocardial infarction and current anginal status were determined for 90 nearly consecutive patients who underwent coronary arteriography at the Johns Hopkins Hospital between 1960 and 1967. All patients had at least one coronary arterial narrowing equal to or greater than 70 percent; 78 of 90 patients would be candidates for coronary bypass surgery by present criteria. Twenty-nine of the 78 surgically "suitable" patients died of cardiac causes; 7 of 49 survivors sustained an acute myocardial infarction (mean follow-up period 9.9 years). Patients with a 70 percent or greater narrowing proximal to the first septal branch of the left anterior descending coronary artery had a significantly greater mortality compared with patients with equivalent narrowing distal to the first septal branch or with patients without 70 percent or greater narrowing of the left anterior descending artery. The patients with a 70 percent or greater narrowing of the left anterior descending artery who died were those with a significant narrowing in at least one other major coronary artery. Multivariate stepwise discriminate function analysis of all clinical, electrocardiographic (except stress electrocardiographic) and arteriographic variables identified three independent predictors of mortality: (1) the simultaneous occurrence of a narrowing in left anterior descending and right coronary arteries, (2) prior myocardial infarction; and (3) 70 percent or greater narrowing proximal to the first anterior descending septal branch. When stress electrocardiographic findings were included, a "positive" stress electrocardiographic test was also an independent predictor of mortality.

The distribution and extent of atherosclerosis within the coronary arterial circulation is an important determinant of subsequent mortality.[1] Although previous reports have shown a relation between survival and extent of atherosclerotic disease[2] or the number of major coronary arteries narrowed,[3–6] the only specific narrowing demonstrated to be associated with a high mortality rate is 50 percent or greater obstruction of the left main coronary artery.[7–11] The patients who underwent coronary arteriography at the Johns Hopkins Hospital between 1960 and 1967 were examined to determine whether a significant narrowing at locations other than the left main coronary artery was associated with a high risk of dying. The relative contribution of historical, electrocardiographic and coronary arteriographic findings to the occurrence of death after arteriography was examined using multivariate stepwise discriminate function analysis.

Methods

Patient group: During the 8 year period between 1960 and 1967, 350 patients underwent selective coronary arteriography at the Johns Hopkins Hospital. Of these patients, 104 were excluded from this study because the origin of their cardiac disease was considered to be primarily valvular or myocardial and not atherosclerotic. In two patients, the arteriogram was unsatisfactory for interpretation. Eighteen other patients were excluded because they underwent internal mammary arterial implantation within 1 year of coronary arteriography.

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Of the remaining 224 patients, 90 had 70 percent or greater narrowing of at least one major coronary artery and might have been considered for coronary bypass grafting if it had been available at the time they underwent arteriography. One hundred thirty-four patients were excluded from the study because no major coronary artery was narrowed by 70 percent or more.

Patient follow-up: Follow-up information on all 90 patients was available through January 1975 either by reexamination of the patient at the Johns Hopkins Hospital or by letter or phone call to the patient or referring physician. If a patient died, the cause and circumstances of death were ascertained from the patient's physician and death certificate. Three patients underwent coronary bypass graft surgery at 44, 65 and 82 months, respectively, after arteriography. The follow-up period for these three patients was only until the time of operation. There were 32 deaths in this series; twenty-nine deaths were considered of cardiac origin and 3 of noncardiac origin. Two patients died of cancer (52 and 83 months, respectively, after arteriography) and one in an automobile accident (27 months after arteriography); they were considered alive until that point and then "lost to follow-up."

Clinical data: The following information was available from the patient's hospital record: age, sex, duration and severity of angina before arteriography, history of a previous myocardial infarction, history of congestive failure, cardiothoracic ratio by chest roentgenogram and fasting serum cholesterol level. Functional disability due to chest pain was defined according to the New York Heart Association classification.[12] Congestive heart failure considered secondary to left ventricular dysfunction was noted by the presence of bilateral pulmonary rales, hepatomegaly or pedal edema, or the presence of orthopnea or paroxysmal nocturnal dyspnea. Standard posteroanterior and lateral chest X-ray films were obtained in all patients. Cardiomegaly was defined as a cardiothoracic ratio of greater than 50 percent on the posteroanterior chest X-ray film.

Electrocardiographic findings: The electrocardiogram at rest was interpreted as normal or abnormal according to the criteria of Rose and Blackburn.[13] An electrocardiogram at rest was considered abnormal if at least one of the following was present: a Q wave of 0.04 second's duration, an S-T segment shift of at least 1 mm (either depression or elevation), left bundle branch block or atrial fibrillation.

A Master double two-step exercise electrocardiographic test was performed in 68 patients at the time of coronary arteriography. None of these 68 patients had evidence of either left ventricular hypertrophy or left bundle branch block in the electrocardiogram at rest that precluded interpretation of the stress electrocardiographic changes. Ten leads were recorded simultaneously before, during and after exercise.[14] The end point of a Master double two-step test was the completion of a specified number of trips across two steps. The number of trips was determined by the patient's sex, age and weight.[15] A stress test was interpreted as positive when the electrocardiogram manifested horizontal or downsloping S-T segment depression of at least 1 mm for 0.08 second on three consecutive beats. Available stress tests were reviewed. If a patient's stress test was not available for review by us, we obtained a report from the hospital record describing the test as positive or negative by these criteria.

Coronary arteriography: Selective coronary arteriography using the brachial arterial (Sones) technique was performed in all patients.[16] Multiple cineradiographs in each patient were reviewed by one author (L.S.C.G.) without knowledge of the patient's subsequent clinical course. The coronary arterial system was divided into 15 segments as proposed by a committee of the American Heart Association,[17] and the most severe luminal narrowing for each segment was recorded (in percent) as (a) 30, (b) 50, (c) 70, (d) 90 or "near-total" occlusion, (e) 100 (or total), or (f) no narrowing or irregularity present. For purposes of analysis, each patient was considered to have one, two or three vessel disease depending on whether the right, left anterior descending or circumflex artery was narrowed by 50 percent or more. Three patients with a narrowing of at least 50 percent of the left main coronary artery were considered to have a narrowing of both the left anterior descending and left circumflex coronary arteries. Because only three patients had significant left main disease and only one died during the follow-up period, dates on these three patients were best analyzed separately.

A schematic drawing of the left main and left anterior descending arteries according to the American Heart Association classification proposal is shown in Figure 1. Patients were considered to have "proximal" left anterior descending disease if there was a 70 percent or greater narrowing proximal to the first septal branch (segment 5 or 6) or "distal" anterior descending disease if such narrowing was in the segment immediately distal to the first septal branch (segment 7). Filling by collateral channels of any coronary segment was also noted.

Left ventriculography was not performed in these patients. This procedure was not a routine part of the catheter evaluation of coronary heart disease at The Johns Hopkins Hospital until 1968. Hence, the influence of left ventricular contraction patterns on survival could not be analyzed in these patients.

Surgical suitability: Ninety patients were classified as "suitable" or "unsuitable" candidates for coronary bypass graft surgery by current 1978 criteria. "Suitability" for such surgery was judged on the basis of three criteria: (1) narrowing of 70 percent or more in at least one major coronary artery; (2) the characteristics of the coronary arterial segment distal to the obstruction, and (3) left ventricular performance. To be suitable for coronary bypass surgery, the distal coronary arterial segment had to be opacified by either anterograde or collateral filling and have an internal diameter of at least 1 mm *and* be free of plaque so that the internal diameter was not

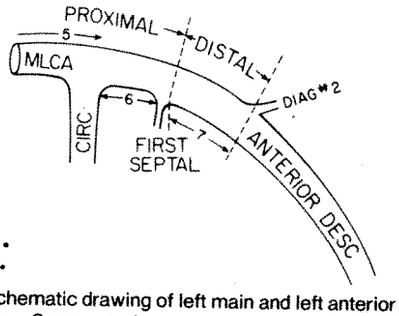


FIGURE 1. Schematic drawing of left main and left anterior descending coronary artery. Segments drawn according to American Heart Association proposal.[15] ANTERIOR DESC = left anterior descending artery; CIRC = circumflex artery; DIAG #2 = second diagonal branch of left anterior descending artery; DISTAL = coronary segment 7 (7) that begins *distal* to origin of first septal branch; FIRST SEPTAL = first septal branch of left anterior descending artery; MLCA = left main coronary artery; PROXIMAL = coronary segments *proximal* to first septal branch (segments 5 and 6; 5 = (segment 5) left main coronary artery; 6 = (segment 6) left anterior descending arterial segment proximal to and including origin of first septal branch; 7 = (segment 7) left anterior descending segment beginning distal to origin of first septal branch and extending to point where it forms an angle in the right anterior oblique projection, often coinciding with the origin of the second diagonal branch.

reduced by 50 percent or more at the usual site of bypass graft and coronary arterial anastomosis or distal to this location. A distal coronary artery was considered unsuitable for bypass surgery if any one of the criteria was absent. A patient was considered "unstable" for bypass surgery on the basis of presumed severe left ventricular dysfunction if the cardiothoracic ratio was greater than 50 percent on the plain chest X-ray film *and* left ventricular end-diastolic pressure was greater than 20 mm Hg *and* the patient had congestive left ventricular failure on clinical examination. These data were reviewed for each patient by one of us (L.S.C.G.) without knowledge of the patient's subsequent clinical course.

Statistical methods: Contingency table analysis utilizing chi-square tests of significance was used to test individually the effect of independent clinical, electrocardiographic or arteriographic variables against the dichotomous outcome of subsequent survival or death. These variables included sex; degree of anginal disability; history of a previous myocardial infarction; history of congestive heart failure; cardiothoracic ratio greater than 50 percent on a chest X-ray film; normality or abnormality of the electrocardiogram at rest and during stress; the number of coronary arteries narrowed by 50 percent or more; presence or absence of 50 percent or greater narrowing of the left main coronary artery or of the right, left anterior descending or left circumflex artery; presence or absence of 70 percent or greater narrowing proximal or distal to the first left anterior descending septal branch; and presence or absence of collateral filling of the distal left anterior descending artery. Continuous variables such as age, cholesterol level and duration of angina before arteriography were similarly compared with Student's *t* test.

To consider the actuarial survival experience, we constructed cumulative survival curves that took into account various lengths of follow-up study. These curves were fitted by the method of Kaplan and Meier.[18] Factors were then examined for their possible effect on survival by comparing these survival curves using Peto's analysis.[19,20]

Multivariate stepwise discriminate function analysis was used to consider simultaneously all independent variables.[21–24] Dichotomous variables, such as male or female or the presence or absence of prior infarction, were entered as 0, 1 variables. Continuous variables, such as age and duration of angina, were used allowing for both linear and nonlinear effects. The coronary arteriographic variables were entered as both continuous and dichotomous variables. Each patient was entered as having 50 percent or greater narrowing of one, two or three arteries. The location of the narrowing 70 percent or greater of the left anterior descending artery as proximal or distal to the first septal branch was entered as a dichotomous variable. The percent narrowing of each of the three major arteries was analyzed as a continuous variable and then reanalyzed as a dichotomous variable separated at 70 percent or greater narrowing. Terms of interaction for interdependence between vessels as well as location of the 70 percent or greater narrowing in the left anterior descending artery were also included in the analysis.

Multivariate stepwise discriminate analysis ranks the independent variables, including the terms of interaction, in order of their contribution to discrimination between those who survive or die and allows for significance testing of the contribution at each step. It is therefore possible to assess whether a variable makes a significant contribution over and above the other factors included. The significance levels derived by this technique are statistical tests of significance by which additional predictive information is provided by a specific variable over and above the information provided by the variables already tested.

Results

Surgical suitability: Of the 224 patients whose data were reviewed, 90 patients had 70 percent or greater narrowing of at least one coronary artery. Twelve of these patients were considered unsuitable candidates for coronary bypass grafting by current criteria because the distal coronary arterial segment or segments were considered unsuitable for grafting (nine patients) or left ventricular function was presumed to be very poor (three patients).

Clinical follow-up: Follow-up information on these 90 patients at a mean interval (± standard error of the mean) of 9.9 ± 0.2 years after coronary arteriography is recorded in Table I. The mortality rate was higher in the 12 patients who were considered unsuitable for coronary bypass grafting (67 percent), compared with the 78 patients who were considered suitable candidates (37 percent). Of the 78 patients who would have been candidates for bypass surgery by current criteria, 29 died of cardiac causes and 49 were alive at the time of follow-up study. Seven (14 percent) of these 49 survivors sustained a nonfatal myocardial infarction after coronary arteriography and 39 (80 percent) continued to have angina pectoris; however, 31 (63 percent) were employed full time.

The 78 patients considered to be surgical candidates have been grouped by the degree of anginal disability at the time of coronary arteriography (Fig. 2). There was

TABLE I

Survival After Coronary Arteriography

	Surgical Candidates*	Not Surgical Candidates*
Patients (n)	78	12
Deaths	29 (37%)	8 (67%)
Acute infarction/survivors	7/49 (14%)	0/4
Continued angina/survivors	39/49 (80%)	3/4 (75%)
Engaged in full-time work/survivors	31/49 (63%)	3/4 (75%)

* See text for description of "surgical" and "not surgical" candidates.

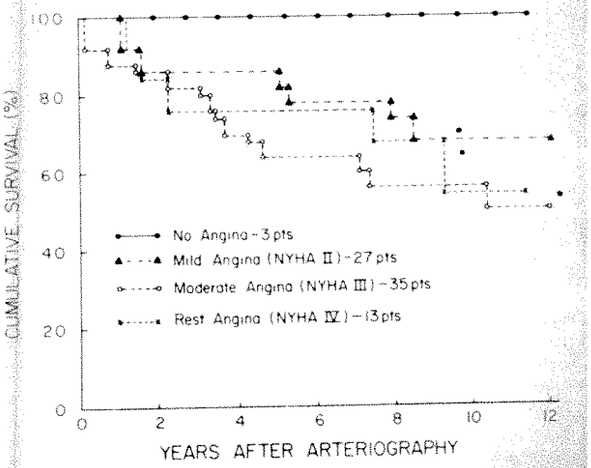


FIGURE 2. Influence of anginal disability on expected cumulative survival. NYHA = New York Heart Association; pts. = patients.

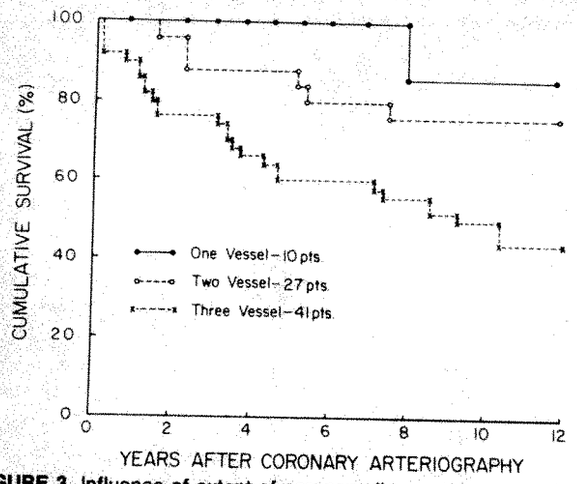


FIGURE 3. Influence of extent of coronary disease on expected cumulative survival. Extent of disease is defined as one, two or three major arteries narrowed by 50 percent or more. pts. = patients.

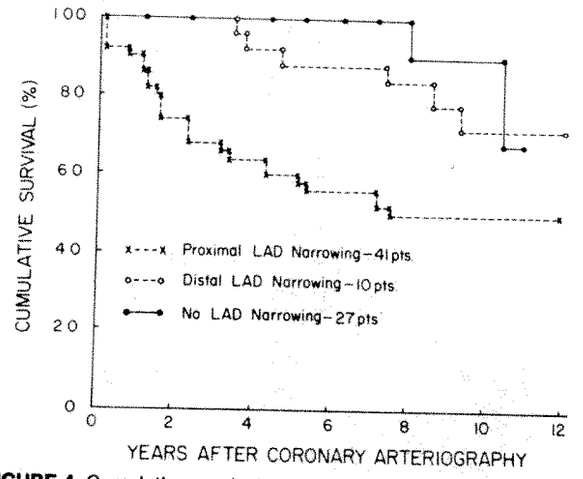
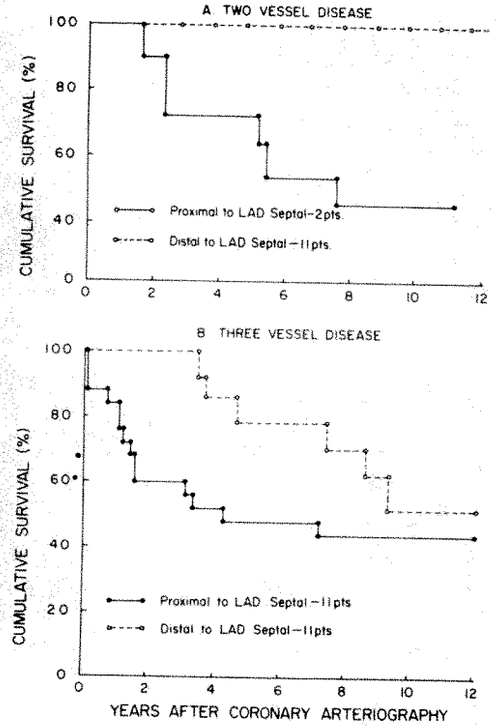


FIGURE 4. Cumulative survival of patients with 70 percent or greater narrowing proximal to the first left anterior descending (LAD) septal branch (41 patients), 70 percent or greater narrowing in a coronary segment distal to the first anterior descending septal branch (27 patients), and those patients without 70 percent or greater narrowing in either the anterior descending or left main coronary arteries (10 patients).

no significant difference in mortality rates among these groups. Mild anginal symptoms (New York Heart Association class II) did not appear to predict improved survival in the 78 patients in this study.

Survival in patients with one, two or three vessel disease: A survival analysis of the 78 patients, based on whether one, two or all three major coronary arteries were narrowed by at least 50 percent, is shown in Figure 3. The mean follow-up period for these patients was 9.9 years. There was a significant difference in these survival curves ($p < 0.02$). Furthermore, the linear trend across the number of vessels was significant ($p < 0.02$). Ten patients had single vessel disease, including seven who had, as the only obstructive lesion, narrowing of the left anterior descending artery proximal to the first septal perforating branch. Only one patient with single vessel disease died. This man had 90 percent narrowing of the left anterior descending artery proximal to the first septal branch. In this small patient group, those with single vessel disease had a good outcome, including those patients with significant narrowing before the first septal branch of the left anterior descending artery.



GURE 5. Cumulative survival of patients with either two vessel (**A.**) three vessel (**B.**) coronary artery disease. Each group is subdivided :cording to whether the 70 percent or greater narrowing is located oximal or distal to the first septal perforator branch of the left anterior :scending (LAD) artery. pts. = patients.

Influence of left anterior descending arterial narrowing on survival: The influence of narrowing of a particular artery on survival after arteriography was examined. Narrowing of the left anterior descending artery by at least 70 percent was found to influence adversely subsequent mortality. (This was true only in the presence of significant disease in at least one other major artery.) Seventy patients were available for follow-up at 8 years. Twenty-four (40 percent) of the 60 patients with 70 percent or greater narrowing of the left anterior descending or left main coronary artery were dead compared with none of the 10 patients with either no or less than 70 percent narrowing of the left anterior descending artery ($p < 0.05$). As will be described later, most of the deaths in patients with a 70 percent or greater narrowing of the left anterior descending artery occurred in those who also had a significant narrowing of at least one other major coronary artery.

Forty-one patients had at least 70 percent narrowing proximal to the first septal branch of the left anterior descending artery; in 38 of the 41 this narrowing was in the anterior descending artery (Fig. 1, segment 6); in 3 it was in the left main coronary artery (Fig. 1, segment

TABLE II

Clinical Findings of Patients With 70 Percent or Greater Narrowing Proximal or Distal to First Septal Branch of Left Anterior Descending Artery

	Proximal (41 patients)	Distal (27 patients)	p
Age (mean ± SD) (yr)	42.1 ± 7.6	43.6 ± 8.1	NS
Male (%)	90	85	NS
Cholesterol (mean ± SD) (mg/100 ml)	284 ± 69	289 ± 83	NS
Prior infarction (%)	34	26	NS
Duration of angina (mean ± SD) (mo)	41.4 ± 43.4	34.1 ± 32.1	NS
Abnormal rest electrocardiogram (%)	59	48	NS

NS = not significant; p = probability; SD = standard deviation.

TABLE III

Collateral Filling of Left Anterior Descending Artery (LAD) and Death Within 8 Years After Arteriography*

Severity of Proximal LAD Narrowing	Collateral Filling of Distal LAD		No Collateral Filling of Distal LAD	
	Cases	Deaths at 8 yr	Cases	Deaths at 8 yr
100% occlusion	12	3 (25%)	0	0
90–99% narrowing	6	5 (83%)	28	10 (37%)
70–89% narrowing	4	4 (100%)	10	2 (20%)
	22	12 (55%)	38	12 (32%)

* Only patients with at least 8 years of follow-up study are included in this table.

5). In 27 patients, the 70 percent narrowing in the anterior descending artery was in segment 7 (Fig. 1) just distal to the origin of the first septal branch. Survival data in these two subgroups as well as in the 10 patients who did not have a 70 percent or greater narrowing in the anterior descending artery are shown in Figure 4. The poorest outcome was associated with narrowing proximal to the first septal branch and the most favorable was noted in patients without significant disease of the anterior descending artery. Patients with anterior descending arterial narrowing distal to the first septal branch has an intermediate outcome ($p < 0.04$). The linear trend across these three variables is significant ($p < 0.02$).

• *The influence of proximal and distal left anterior descending arterial disease* was examined separately in patients with two and three vessel disease (Fig. 5). Although the patient groups are small and statistically significant differences in survival were found only in the group with two vessel disease, mortality was greater in patients with disease of the proximal left anterior descending artery in both groups.

The clinical characteristics were compared in the 41 patients with 70 percent or greater narrowing proximal to the first septal branch and in the 27 patients with significant narrowing distal to this branch (Table II). There were no significant differences between these two groups with respect to age, sex, history of prior myocardial infarction or duration of angina before arteriography, presence of an electrocardiographic abnormality at rest or serum cholesterol level.

Collateral filling of left anterior descending artery: Of the 68 patients with at least 70 percent narrowing of the left anterior descending or left main coronary artery, 24 had collateral filling of the distal anterior descending artery from either the left circumflex or the right coronary artery and 44 patients did not. Fourteen (58 percent) of the 24 patients with collateral filling of the distal anterior descending artery died during the follow-up period compared with 12 (27 percent) of the 44 patients without collateral vessels to the left anterior descending artery. Survival analysis of these two patient groups revealed a significantly higher mortality rate among patients with collateral filling of the left anterior descending artery than on patients without collateral vessels ($p < 0.04$) (Fig. 6). The severity of the proximal narrowing of the left anterior descending artery in these two groups and the number of patients who died within each group after arteriography are shown in Table III. The number of patients with a total occlusion of the proximal left anterior descending artery was larger in the group with collateral vessels. Nevertheless, the presence of collateral vessels to the distal vascular segment may be an angiographic marker of more "severe" disease and not necessarily provide increased protection against death.

Electrocardiogram at rest: Of the 78 surgically suitable patients, 44 had an abnormal electrocardiogram at rest at the time of coronary arteriography. Twenty patients had a Q wave, 19 had an S-T segment shift of more than 1 mm, 4 had left bundle branch block and 1 had atrial fibrillation. When all four groups are considered as having an abnormal electrocardiogram at rest, survival analysis shows that there was greater mortality in patients with an abnormal electrocardiogram at rest than in patients with a normal electrocardiogram ($p < 0.03$) (Fig. 7).

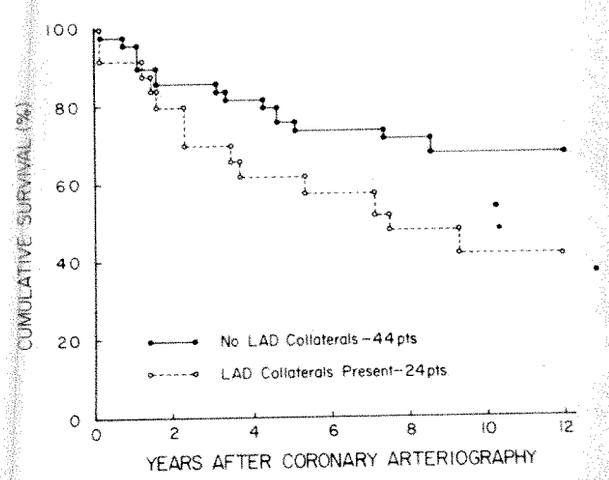


FIGURE 6. Cumulative survival of patients with 70 percent or greater narrowing in the left main or left anterior descending (LAD) coronary artery who have collateral vessels (24 patients) and those who do not have collateral vessels (44 patients) to the distal anterior descending artery on arteriography.

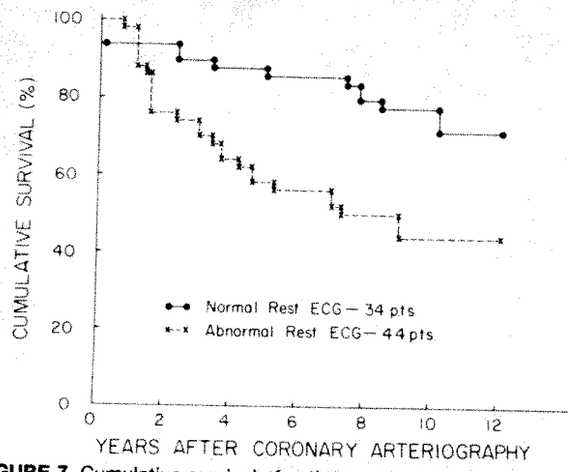


FIGURE 7. Cumulative survival of patients with either a normal or an abnormal electrocardiogram at rest (ECG). pts. = patients.

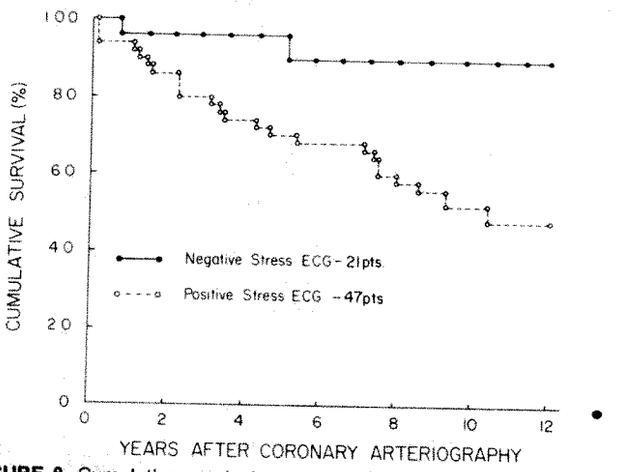


FIGURE 8. Cumulative survival of patients (pts.) with a negative or positive stress electrocardiogram (ECG).

Stress electrocardiogram: Sixty-eight of the 78 surgically suitable patients underwent a double Master's exercise electrocardiogram. Analysis of survival revealed a poorer outcome in patients with a positive stress electrocardiogram than in those with a negative stress test ($p < 0.02$) (Fig. 8). Fifty-eight of the 68 patients with 70 percent or greater narrowing in the left main or left anterior descending coronary artery underwent stress electrocardiography. These patients were subclassified according to whether the 70 percent or greater narrowing was proximal or distal to the first anterior descending septal branch, and whether the stress test was positive or negative for S-T segment shift. Survival analysis showed the poorest outcome in patients with a 70 percent or greater narrowing in the proximal left anterior descending artery and a positive stress test and the best outcome in patients with a 70 percent or greater narrowing of the distal anterior descending artery and a negative stress test. The outcome in patients with a narrowing of the proximal anterior descending artery but with a negative stress test and of those with a distal narrowing but with a positive stress test was intermediate ($p < 0.02$). (Fig. 9).

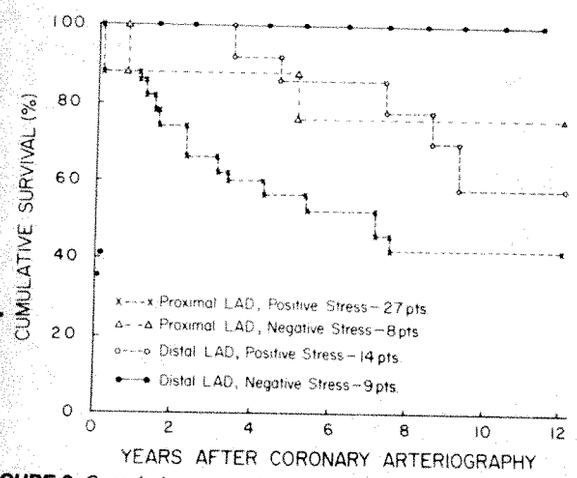


FIGURE 9. Cumulative survival of patients with 70 percent or greater narrowing proximal to the first septal perforator branch of the anterior descending artery and a positive (27 patients) or negative (8 patients) stress electrocardiogram; 70 percent or greater narrowing in segment distal to the first septal branch and a positive (14 patients) or negative (9 patients) stress electrocardiogram. LAD = left anterior descending coronary artery.

Multivariate analysis: Many independent variables when considered separately were noted to have an influence on survival. A multivariate stepwise discriminate analysis of all clinical, electrocardiographic and coronary arteriographic variables was to assess simultaneously the relative contribution of each variable to prediction of overall survival. Two analyses were performed. Because only 68 patients underwent stress electrocardiography, data on all 78 patients were first analyzed without stress electrocardiographic findings. Then data on the 68 patients who had a stress test were separately analyzed. The percent narrowing in each major artery was entered into each multivariate analysis as both a continuous variable (30, 50, 70, for example) and a dichotomous variable with percent narrowing being either 70 percent or greater or less than 70 percent. Because the analysis that used the narrowing as a continuous variable gave a somewhat better prediction for survival, only this analysis is presented.

When all input variables except the stress electrocardiographic findings were considered (78 patients), a combination of three variables was found to be predictive of subsequent death. These were, in order of degree of predictivity: (1) the simultaneous occurrence of narrowing in the right coronary artery and in the left anterior descending artery (either segment 6 or segment 7); (2) history of a myocardial infarction before arteriography; and (3) the presence of a 70 percent or greater narrowing proximal to the first anterior descending septal branch (Table IV). No other variables added significantly to the ability to predict mortality in this analysis.

When the stress electrocardiographic findings were included (68 patients), the variables that were most predictive of subsequent death included: (1) the percent narrowing in the right coronary artery simultaneous with the presence of a 70 percent or greater nar-

TABLE IV

Prediction of Mortality by Multivariate Stepwise Discriminate Function Analysis of all Variables Except Stress Electrocardiography [alive (n = 49); dead (n = 29); total (n = 78)]

Step	Variable Entered	Correctly Predicted Alive	Correctly Predicted Dead	Total Correctly Predicted	p*	Incorrectly Predicted Alive	Incorrectly Predicted Dead
1	RCA × LAD†	27 (55%)	22 (76%)	49 (63%)	<0.001	7	22
2	Prior MI	37 (76%)	22 (76%)	59 (76%)	<0.01	7	12
3	Proximal LAD 70% or greater narrowing	36 (74%)	22 (76%)	58 (74%)	<0.05	7	13

* p significance level of contribution of prediction for each variable. Although each variable does not appreciably alter the percent of correct predictions, the precision of the estimate of the percent is enhanced by the level shown. † Simultaneous narrowings in the right (RCA) and left anterior descending (LAD) coronary arteries. Interaction variable where percent narrowings in both arteries were entered as continuous variables.
MI = myocardial infarction.

rowing proximal to the first anterior descending septal branch; (2) a positive stress electrocardiographic test; (3) history of a myocardial infarction before arteriography; and (4) percent narrowing in the left circumflex artery simultaneous with the presence of a 70 percent or greater narrowing distal to the first anterior descending septal branch (Table V). No other variable in this patient group, including anginal status, electrocardiographic findings at rest, the extent of coronary disease, the presence of collateral vessels to the anterior descending artery, contributed significantly to the prediction of subsequent survival.

In Tables IV and V, the variable shown in step 1 was the best predictor of patients who were alive and those who died. Step 2 shows the variable with the next highest predictive value. The probability (p) values represent statistical significance in achieving this prediction. For convenience, it is helpful to examine the percent correctly predicted at each step. For example, in step 1 in Table V, the simultaneous occurrence of 70 percent or greater narrowing in the proximal left anterior descending artery and in the right coronary artery correctly identified 16 of 24 patients who died whereas the absence of one or both of these variables correctly predicted 33 of 44 patients who were alive at follow-up study. Hence, the outcome of 49 of 68 patients was correctly predicted by the simultaneous presence of these two variables.

Discussion

This study of the natural history of patients with coronary heart disease was prompted by two questions: (1) the relative contribution to survival of the many clinical, electrocardiographic and coronary arteriographic variables available to the physician at the time of cardiologic evaluation; and (2) the mortality, rate of nonfatal infarction and symptomatic status of patients who have not undergone any cardiac revascularization procedure, but who are comparable with persons now considered for coronary bypass surgery. Previous natural history studies have not made suitability for such surgery a criterion for inclusion.

Independent predictors of prognosis: Several investigators[3–5,25] have reported a greater risk of death in patients with significant left anterior descending arterial disease than in those whose disease is limited to either the left circumflex or the right coronary artery or both arteries. Our study confirms this finding. Virtually all of the deaths in our study occurred in patients with disease of the left anterior descending coronary artery. Because significant disease of this artery is very common among symptomatic patients with coronary disease, the presence of a 70 percent or greater narrowing in this vessel did not, by itself, discriminate between those who would live and those who would die. Multivariate analysis of the entire patient group (without

TABLE V

Prediction of Mortality by Multivariate Stepwise Discriminate Function Analysis of all Variables Including Stress Electrocardiography [alive (n = 44); dead (n = 24); total (n = 68)]

Step	Variable Entered	Correctly Predicted Alive	Correctly Predicted Dead	Total Correctly Predicted	p*	Incorrectly Predicted Alive	Incorrectly Predicted Dead
1	Proximal LAD ≥ 70% narrowing × RCA†	33 (75%)	16 (67%)	49 (72%)	<0.001	8	11
2	Positive stress electrocardiogram	34 (77%)	16 (67%)	50 (74%)	<0.01	8	10
3	Previous MI	33 (75%)	18 (75%)	51 (75%)	<0.05	6	11
4	Distal LAD ≥70% narrowing × LCx‡	35 (80%)	19 (79%)	54 (79%)	<0.05	5	9

* p significance level of contribution of prediction for each variable. Although each variable does not appreciably alter the percent of correct predictions, the precision of the estimate of the percent is enhanced by the level shown. † Simultaneous narrowing of 70 percent or greater in the proximal left anterior descending artery (LAD) and a narrowing in the right coronary artery (RCA) (entered as a continuous variable). ‡ Simultaneous narrowing of 70 percent or greater in the distal left anterior descending artery and a narrowing in the circumflex artery (entered as a continuous variable).
MI = myocardial infarction.

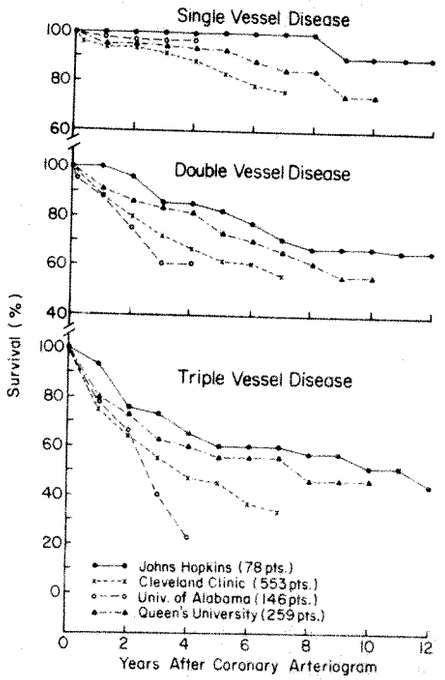


FIGURE 10. Cumulative survival of patients with one, two or three major coronary arteries narrowed by 50 percent or greater. Data from three previous studies[30–32] as well as from this report are included. pts. = patients.

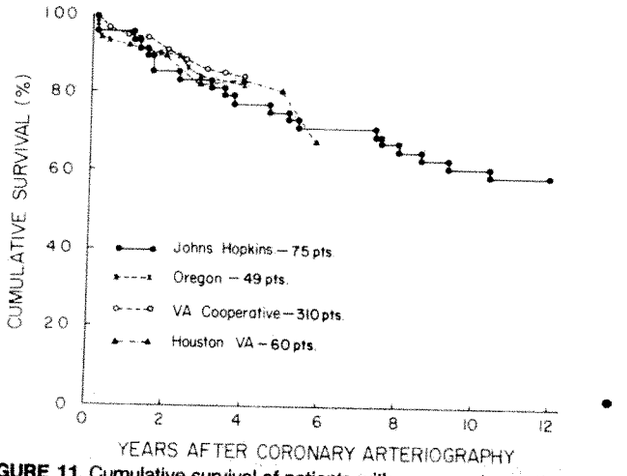


FIGURE 11. Cumulative survival of patients with coronary heart disease who were surgically "suitable" but followed up with medical therapy. Data from three prospective randomized studies of medical versus surgical therapy[27,28,34] as well as from this report are included. pts. = patients.

stress electrocardiographic findings) demonstrated that two anatomic situations independently placed a patient at high risk of dying. The first was the simultaneous narrowing of both the left anterior descending and the right coronary arteries; the second was the presence of a 70 percent or greater narrowing proximal to the first anterior descending septal branch. The only other variable that independently contributed to predicting survival for the entire group was the history of a myocardial infarction before arteriography. When the results of stress electrocardiography were considered, this variable was also found to be a significant independent predictor of survival. Thus, multivariate analysis emphasizes the importance of considering not only clinical and electrocardiographic data at rest in assessing patient prognosis, but also the findings of coronary arteriography and stress electrocardiography.

Prognosis of surgically suitable patients treated medically: The ideal study to determine subsequent survival with medical therapy of patients suitable for coronary bypass grafting is to allocate these patients randomly to either medical or surgical therapy after coronary arteriography. Whereas at least four such prospective studies are currently underway,[26–29] the long-term results will not be known for several years. An alternative approach is to review the natural history of suitable patients who underwent coronary arteriography before the availability of coronary bypass grafting.

"Suitability" for coronary bypass graft surgery was an important criterion for selecting patients included in this natural history study. Thirteen percent of the patients with significant (at least one artery narrowed by 70 percent or more) obstructive coronary disease were excluded from this study because of diffuse distal coronary disease or presumed very poor left ventricular function. A patient who is judged suitable for coronary bypass surgery is likely to have a more favorable prognosis than the patient with more extensive coronary disease or severe left ventricular dysfunction. This may be the reason why survival in our series is better than that reported by three other centers[30–32] (Fig. 10). During the period that the series at Queen's Hospital[32] and the Cleveland Clinic[30] were accumulated, the operation of choice for patients with coronary atherosclerosis was implantation of the internal mammary artery. It is possible that many patients with a more favorable coronary and left ventriculographic anatomy underwent this procedure while the medical treatment group included a higher percent of patients with more extensive coronary or left ventricular disease, or both. Neither of these reports indicates why some patients were referred for surgery and other patients were not. Although implant surgery was not routinely performed at the University of Alabama[31] during the period that the 206 patients in that series underwent arteriography, there was no attempt to exclude patients with diffuse distal coronary disease or very poor left ventricular function who might not be suitable candidates for coronary bypass surgery by current criteria.

The cumulative survival of patients in our series is very comparable with that of the surgically suitable but medically treated patients in the Veterans Administration Cooperative,[33] Houston Veterans Administration[27] and the University of Oregon[28] studies (Fig. 11). When survival of patients with one, two or three vessel disease is examined separately, the cumulative survival of the patient subgroups in our series is similar to that of the Veterans Adminstration Cooperative Study.[33] Although not included in Figure 11, the expected survival of an age-matched patient group drawn from the general population is better than any of the patient groups with coronary heart disease. Expected survival

in a normal 43 year old man for the next 4, 8, and 12 years is 98, 95 and 90 percent, respectively.[34]

Left anterior descending arterial stenosis proximal versus distal to the first septal perforating branch: There are at least two possible reasons why a patient with significant (70 percent or greater) narrowing proximal to the first septal perforating branch may be at a higher risk of mortality. First, narrowing proximal to the first septal perforating branch is very often also proximal to, or involves the origin of, the first diagonal branch of the anterior descending artery. Hence, three sizable myocardial segments including the interventricular septum, the myocardium perfused by the first diagonal branch and the distal main stem left anterior descending artery are jeopardized by a narrowing at this location. A second possible reason for the increased mortality associated with narrowing proximal to the first septal branch relates to the importance of regional ischemia or infarction of the interventricular septum, a situation that may predispose to ventricular arrhythmia and conduction defects. Among our patients who died, 15 of the 19 sudden cardiac deaths in our series were noted in those patients with a significant narrowing proximal to the first septal branch. Further study is needed to understand these two possibilities. Nevertheless, the outcome in the seven patients in our study with single vessel disease involving only the anterior descending artery proximal to the first septal branch was very favorable. Although a 70 percent narrowing of the anterior descending artery at this location was a significant independent predictor of survival, an even more powerful predictor was the simultaneous presence of disease in the right and left anterior descending artery. Thus, two important factors may contribute to survival: (1) narrowing proximal to the first septal branch and (2) significant narrowing in at least one other major coronary artery.

Differences from previous studies: Hammermeister et al.[35] in Seattle and more recently Harris et al.[36] reported follow-up studies that used multivariate discriminate analysis to define predictors of survival in patients treated medically. The findings of these two studies and their approach are very similar to those used in our report. Three important differences between these two studies and ours should be noted. First, the study populations of the Seattle and Duke series are different from that of our series: Both the Seattle and Duke series included patients who were considered for coronary bypass surgery but who did not undergo this procedure. In the Seattle series, the patients treated nonsurgically represented 28 percent of those who entered the registry. In the Duke series, 61 percent of the patients who underwent coronary arteriography were treated nonsurgically for at least 6 months. Ten percent of this "medical" group subsequently underwent coronary bypass surgery and were considered alive but removed from follow-up study at the time of operation. No information is available concerning why these medically treated patients were not referred for surgery although important differences between the medical and surgical cohorts were previously described.[37,38] The second difference between our study and those reported by the Seattle and Duke groups was the availability of ventriculography either to calculate left ventricular ejection fraction or to describe ventricular contraction patterns. The ejection fraction is the best single method to describe left ventricular function, but other variables, including the history of a prior myocardial infarction, electrocardiographic abnormalities at rest, congestive heart failure and heart size on chest X-ray film are indirect measures of left ventricular function and are included in our study. The single most important determinant of ejection fraction in patients with coronary artery disease is the history of a prior infarction. In our study, the history of a prior myocardial infarction was an independent predictor of survival.

The third difference involves the use of slightly different statistical techniques. In describing coronary anatomy, both the Seattle and Duke groups entered the extent of coronary disease as a dichotomous variable divided at the 70 percent or 75 percent level, whereas we used percent narrowing as a continuous variable. Also, we made use of interaction terms to describe disease in two vessels simultaneously or at a specific locus within the left anterior descending artery. Finally, the Seattle and Duke studies described outcome as a 2 or 3 year time-dependent survival rate reflecting variations throughout the study in both time in the study and number of deaths. This procedure appropriately necessitates the use of Cox's hazard function analysis.[39] However, in our long-term follow-up study, all patients were followed up approximately 10 years, and the goal of the multivariate analysis was to predict any death regardless of when it occurred. For this reason, discriminate function analysis treating death as a time-independent process was used.

Clinical implications: This study using multivariate analysis has determined that two arteriographic and two clinical findings independently contribute to patient survival. These are (1) the simultaneous presence of significant disease in both the left anterior descending and right coronary arteries; (2) the presence of a 70 percent or greater narrowing of the left anterior descending artery proximal to the first septal perforator branch; (3) the history of a prior myocardial infarction; and (4) a positive stress electrocardiographic test. Left ventriculography was not performed in these patients. Hence, the influence of left ventricular contraction patterns or ejection fraction on subsequent survival could not be analyzed as separate variables in this group of patients.

Because the pattern of coronary atherosclerosis is an important predictor of survival, one objective of future studies will be to identify by noninvasive methods, such as exercise electrocardiography or thallium-201 myocardial scintigraphy or radionuclide ventriculography, those patients with significant arterial narrowings at these locations.

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Merits of Stress Thallium-201 Myocardial Perfusion Imaging In Patients With Inconclusive Exercise Electrocardiograms: Correlation With Coronary Arteriograms

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Stress thallium-201 myocardial perfusion images were obtained in 65 patients with an inconclusive exercise electrocardiogram. All 65 patients underwent coronary angiographic studies. The exercise electrocardiogram was judged inconclusive in 35 patients (54 percent) because submaximal exercise had been performed and in 30 patients (46 percent) who manifested ST-T segment abnormalities at rest. Exercise thallium-201 myocardial perfusion images were abnormal in 20 patients and normal in 45. Nineteen (95 percent) of the 20 patients with abnormal exercise images had severe disease of one or more major coronary arteries. Thirty-seven (82 percent) of the 45 patients with normal exercise images had no significant coronary artery disease; the remaining 8 patients had coronary artery disease. Therefore, 19 of 27 patients with coronary artery disease had abnormal exercise images (sensitivity 70 percent), and 37 of 38 patients without coronary artery disease had normal exercise images (specificity 97 percent). Thallium-201 imaging predicted the correct diagnosis in 56 patients (86 percent). Thus, exercise myocardial imaging with thallium-201 appears to be a useful diagnostic aid in patients with an inconclusive exercise electrocardiogram.

Treadmill exercise testing is widely used as an effective noninvasive diagnostic tool to detect coronary artery disease.[1–5] Several studies have shown a high sensitivity and specificity in preselected patients, particularly those in whom the exercise testing was performed under optimal conditions.[1–4] Exercise test results interpreted as inconclusive or nondiagnostic because of inadequate heart rate response, S-T abnormalities in the electrocardiogram at rest, presence of bundle branch block or a pattern of left ventricular hypertrophy have often been excluded from these reports; therefore, the actual prevalence of inconclusive test results is difficult to ascertain from existing information. A few reports[1,4,6,7] have indicated the occurrence of "indeterminate" or "equivocal" test results in 15 to 30 percent of all patients undergoing treadmill exercise testing.[1,4,6,7]

There is now sufficient reported evidence[6–11] to indicate that exercise thallium-201 myocardial perfusion scintigraphy is an extremely useful procedure in patients suspected of having coronary artery disease. However, only a few studies[7,11] have specifically examined the merits of this procedure in patients with an inconclusive exercise electrocardiogram.

The purposes of this study were (1) to define the incidence of inconclusive exercise treadmill test results, and (2) to evaluate exercise thallium-201 myocardial imaging as a means of detecting coronary artery disease in patients with such test results.

Methods

Patients: For 18 months, 400 patients were studied with a combination of treadmill exercise testing and exercise thallium-201 imaging. In the same period,

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1,174 more patients underwent treadmill exercise testing alone. The exercise electrocardiogram was inconclusive in 146 (36.5 percent) of the 400 patients and in 419 (35.6 percent) of the 1,174 patients. On the recommendation of their physician, 65 of the 146 patients who had undergone both noninvasive procedures underwent cardiac catheterization and coronary arteriography. These 65 patients constitute the group we studied.

Of the 65 patients studied, 40 were men and 25 women (Table I); their average age was 51 years (range 27 to 67). Twenty-six patients (40 percent) had classic angina pectoris, 30 (46 percent) had atypical angina and 9 (14 percent) were asymptomatic and were studied because of a strong family history of coronary artery disease. The resting 12 lead electrocardiogram was normal in 28 patients (43 percent), revealed ST-T wave abnormalities in 33 patients (51 percent) and showed abnormal Q waves indicative of old transmural infarction in 4 patients (6 percent). No patient had electrocardiographic evidence of left ventricular hypertrophy, bundle branch block or preexcitation syndrome, findings that are known to predispose to an inconclusive exercise electrocardiogram.

Treadmill exercise testing: All patients exercised in the fasting state in accordance with a standard Bruce protocol for treadmill exercise testing.[12] Thirty-five patients (58 percent) were receiving propranolol and 12 (18 percent) were receiving cardiac glycosides at the time of the study. Each patient exercised until (1) at least 85 percent of the maximal predicted heart rate for age and condition was reached; or (2) there was 2 mm of downsloping or horizontal S-T segment depression in the absence of a resting S-T abnormality, with or without angina pectoris; or (3) the patient complained of excessive fatigue, leg weakness or shortness of breath; or (4) hypotension, ventricular arrhythmia or dizziness occurred. Three standard electrodardiographic leads (V_1, V_5 and a VF) were continuously monitored. A complete 12 lead electrocardiogram was obtained in each patient immediately after termination of the exercise test.[13]

The exercise electrocardiogram was considered inconclusive in this study when (1) the patient did not achieve 85 percent of the predicted maximal heart rate for age and condition in the absence of diagnostic electrocardiographic changes, or (2) there was S-T segment depression of 0.5 mm or more at rest without an additional 2 mm of S-T depression during exercise.

An exercise treadmill test was considered positive if one or more of the following electrocardiographic criteria were met: (1) 1 mm or greater horizontal or downsloping S-T depression in the absence of a resting S-T abnormality; or (2) 1.5 mm or greater S-T depression 80 ms after the J point, with a slowly rising S-T slope (1 mv/s or less), in the absence of a resting S-T abnormality[14]; or (3) 2 mm of additional horizontal or downsloping S-T depression in the presence of S-T depression in the electrocardiogram at rest.[15] The exercise electrocardiogram was considered negative when the patient achieved 85 percent of the predicted maximal heart rate and there were no ischemic S-T changes. The exercise electrocardiograms were interpreted independently by two observers without knowledge of the results of thallium-201 myocardial perfusion scanning or coronary angiography.

Thallium-201 myocardial imaging: Before these exercise tests were performed, an angiographic catheter was inserted into an antecubital vein and attached to a solution of dextrose in water for flushing. At peak exercise 2 mCi of thallium-201 was injected intravenously and flushed with dextrose and water. The patient was then requested to continue exercising for 30 to 60 seconds more.[16]

Myocardial imaging was performed within 10 to 15 minutes after thallium injection by means of a commercially available scintillation camera equipped with a high resolution parallel hole collimator. Images were obtained in the anterior, 45° left anterior oblique and left lateral projections. Final images were interpreted after background correction (20 to 25 percent) without computer smoothing.

Images were considered normal when there was homogeneous distribution of activity in all segments of the left ventricle. They were considered abnormal when there was partial or complete absence of activity in one or more segments in the known distribution of the coronary arteries.

In patients with abnormal exercise imaging results, redistribution studies were performed in the projection indicating the abnormality 4 hours after the initial study. The images were considered positive when the perfusion defect was seen in the stress study but was absent in the redistribution images, or when the defect in the stress study was larger than that in the redistribution study. Images were interpreted independently by two observers without prior knowledge of the results of exercise electrocardiography or angiography.

Cardiac catheterization and angiography: Each patient underwent left and right heart catheterization in the fasting

TABLE I

Clinical, Electrocardiographic and Angiographic Results in 65 Patients With Inconclusive Exercise Electrocardiograms

	Patients With CAD (n = 27)		Patients Without CAD (n = 38)	
	n	%	n	%
Age (range; mean) (yr)	30–67; 52		27–71; 51	
Male/female ratio	21:6		19:19	
Angina pectoris				
Typical	20	74	6	16
Atypical	6	22	24	63
Absent	1	4	8	21
12 lead ECG				
Normal	12	44	16	42
ST-T changes	11	41	12	58
Q waves	4	15	0	0
Drug therapy				
Propranolol	14	52	21	55
Digitalis	5	19	7	18
Cause of inconclusive exercise ECG				
Submaximal stress	16	59	19	50
Resting ST-T depression	11	41	19	50

CAD = coronary artery disease; ECG = electrocardiogram.

state within 6 months of the exercise studies. Left ventriculography was performed in a 30° right anterior oblique projection or in biplane right and left anterior oblique projections. The contraction pattern was assessed qualitatively for wall motion abnormalities; hypokinesia was defined as reduced motion, akinesia as absence of motion and dyskinesia as a paradoxic systolic bulge. Selective coronary arteriography was performed in multiple projections; when indicated, special cranial and caudal sagittal oblique projections were used.

Significant coronary artery disease was considered present when there was 70 percent or more narrowing in the diameter of one or more of the major coronary arteries (the left main, left anterior descending, left circumflex or right coronary artery) or in one or more of the secondary branches of the left coronary system (marginal or posterolateral branches of the left circumflex artery and diagonal branches of the left anterior descending artery). Collateral channels were considered present when there was delayed opacification of a vessel beyond the site of narrowing or occlusion. The cine films were reviewed independently by two cardiologists without prior knowledge of the results of exercise electrocardiography or thallium imaging.

The consensus of the two observers was used in the analysis of the results of the exercise electrocardiograms and coronary angiograms. There was total agreement between the two observers in the interpretation of the thallium-201 images in 60 of the 65 patients and disagreement on some minor points in 5. The independent interpretation of a third observer was sought in the latter cases and the final determination was made on the basis of agreement of two of the three observers.

Definition of terms: The following definitions are used in the study:

Sensitivity:

$$\frac{\text{True positive}}{\text{True positive + False negative}} \times 100$$

Specificity:

$$\frac{\text{True negative}}{\text{True negative + False positive}} \times 100$$

Predictive positive value:

$$\frac{\text{True positive}}{\text{True positive + False Positive}} \times 100$$

Predictive negative value:

$$\frac{\text{True negative}}{\text{True negative + False negative}} \times 100$$

True positive: Patient with coronary artery disease and an abnormal thallium-201 exercise scan.

True negative: Patient with no coronary artery disease and a normal thallium-201 exercise scan.

False positive: Patient with no coronary artery disease and an abnormal thallium-201 exercise scan.

False negative: Patient with coronary artery disease and a normal thallium-201 exercise scan.

Results

Angiographic findings (Table I): Twenty-seven of the 65 patients had coronary artery disease. In 21 patients, the disease involved one or more of the major coronary arteries: one vessel in 8 patients, two vessels in 8 and three vessels in 5. In the remaining six patients, disease was limited to the secondary branches of the left coronary system. Collateral channels were present in 18 patients (67 percent). The left ventriculogram in patients with coronary artery disease was normal in 9 patients but showed mild hypokinesia in 13 patients and segmental akinesia or dyskinesia in 5 patients. Of the 27 patients with coronary artery disease 20 (74 percent) had typical angina pectoris, 6 (22 percent) had atypical angina and 1 had no angina. The remaining 38 patients had no significant coronary artery disease; of these, only 6 (16 percent) had typical angina, whereas 24 (63 percent) had atypical angina and 8 had no angina.

Electrocardiographic exercise test findings: All 65 patients had an inconclusive exercise electrocardiogram because of submaximal exercise performed or S-T segment abnormalities at rest. None of the patients with S-T abnormalities at rest had an additional 2 mm of horizontal or downsloping S-T depression on exercise. Of the 35 patients whose exercise electrocardiogram was inconclusive because of submaximal stress, 20 (57 percent) were receiving propranolol and 5 (14 percent) were receiving cardiac glycosides; similarly, of the 30 patients whose exercise electrocardiogram was inconclusive because of resting S-T abnormalities, 15 (50 percent) were receiving propranolol and 7 (23 percent) were receiving cardiac glycosides (difference not significant).

Exercise thallium-201 imaging: Twenty of the 65 patients had a positive exercise thallium-201 myocardial imaging result. Of these, 19 (95 percent) had severe coronary artery disease (Fig. 1 to 3). All 20 patients underwent a redistribution study, which showed partial or complete filling of the defects in each patient. Persistent but smaller defects in the delayed images were observed in eight patients; three patients had akinetic or dyskinetic segments, three had hypokinetic segments and two had no wall motion abnormalities. The abnormal exercise images were present in 12 (75 percent) of the 16 patients with an inadequate heart rate response during exercise and in 7 (64 percent) of the 11 patients with resting S-T abnormalities (difference not significant).

Forty-five patients had normal findings on exercise thallium-201 myocardial imaging. Thirty-seven (82 percent) of these patients had either completely normal coronary angiograms (30 patients) or less than 50 per-

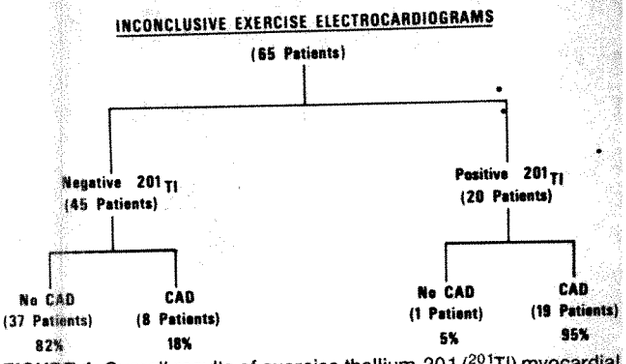


FIGURE 1. Overall results of exercise thallium-201 (^{201}Tl) myocardial perfusion scintigraphy in 65 patients with an inconclusive exercise electrocardiogram. Nineteen of 20 patients with a positive (abnormal) thallium imaging result had coronary artery disease (CAD), and 37 of 45 patients with a negative (normal) thallium imaging results had no coronary artery disease.

cent narrowing of one vessel (7 patients) (Fig. 1). Of the remaining eight patients, six had coronary artery disease limited to the secondary branches of the left coronary system. (In four patients the disease was limited to the marginal branch of the left circumflex artery, and in two there was disease of a marginal branch plus a diagonal branch of the left anterior descending artery.) In contrast, all 19 patients with abnormal exercise images had disease of the major coronary arteries.

These data can be stated in a different way: Only 1 of the 38 patients without coronary artery disease had a positive exercise thallium-201 imaging result (specificity 97 percent). Of the 27 patients with coronary artery disease, 19 had a positive imaging result (sensitivity 70 percent). Thallium-201 imaging predicted the correct diagnosis in 56 (86 percent) of the total group of 65 patients with an inconclusive exercise electrocardiogram; it had a predictive positive value of 95 percent and a predictive negative value of 82 percent.

Comparison of results with those of patients with a conclusive treadmill exercise electrocardiogram: The results are similar to our experience in 123 patients (65 patients with and 58 without coronary artery disease) with a conclusive (either positive or negative) treadmill exercise electrocardiogram (unpublished data). In that series, 52 (80 percent) of the 65 patients with coronary artery disease had abnormal exercise images and 56 (97 percent) of the 58 patients without coronary artery disease had normal exercise images. Of the 52 patients with abnormal exercise images and coronary artery disease 38 (73 percent) manifested perfusion abnormalities at a submaximal exercise heart rate; the exercise electrocardiogram was positive in these patients at a submaximal exercise heart rate. This finding is comparable with the results of the present study, which showed that 12 (75 percent) of 16 patients with coronary artery disease manifested exercise-induced perfusion abnormalities at a submaximal heart rate; however, the exercise electrocardiograms in this latter group of patients failed to show ischemic S-T changes.

Thus, exercise thallium-201 imaging in the patients with a conclusive exercise electrocardiogram had a sensitivity of 80 percent, a specificity of 97 percent and an accuracy rate of 88 percent. In the total group of 123 patients, the exercise electrocardiogram was positive in 48 (74 percent) of the 65 patients with coronary artery disease and negative in 50 (86 percent) of the 58 patients without such disease. The exercise electrocardiogram in the 123 patients had a sensitivity of 74 percent, a specificity of 86 percent and an accuracy rate of 80 percent.

Discussion

Causes of inconclusive treadmill exercise tests: Our findings suggest that treadmill exercise test results are inconclusive in 36 percent of all such tests performed at our institution. The two most common reasons were inadequate heart rate response (54 percent) (Fig. 2) and the presence of S-T depression in the electrocardiogram at rest (46 percent) (Fig. 3).

Although S-T depression on exercise that is at least 2 mm greater than that measured at rest has been reported to indicate a possible abnormal response, none of our patients with S-T depression at rest achieved an additional 2 mm of depression on exercise. Various cardiac and noncardiac medications are known to produce S-T depression. Only seven patients with resting S-T depression in our study were receiving cardiac glycosides. Fifty-seven percent of the patients with an

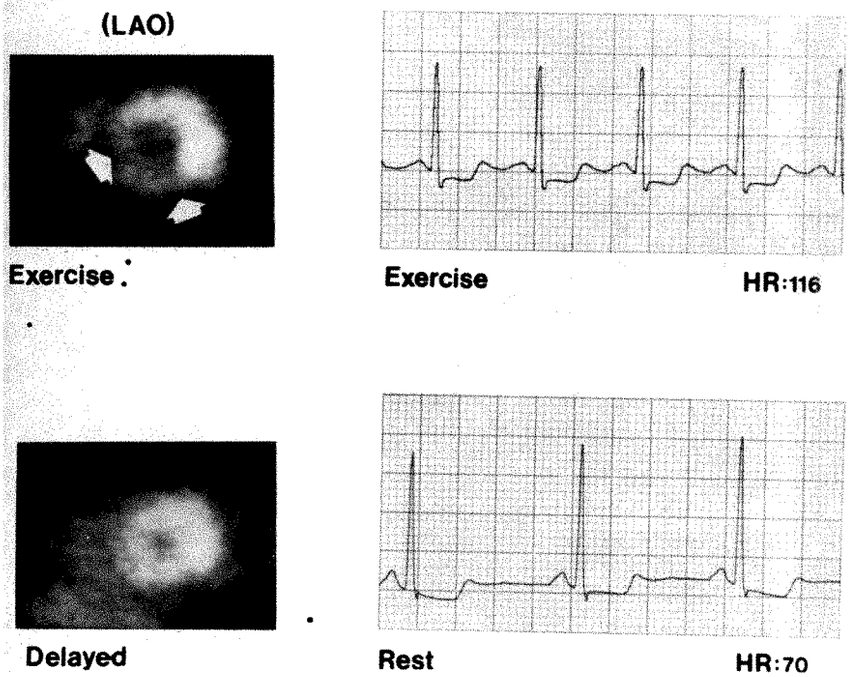


FIGURE 2. Exercise and delayed electrocardiograms and thallium-201 myocardial perfusion scans in a 48 year old woman with chest pain and two vessel coronary artery disease. Electrocardiographic lead V_5 shows S-T segment depression at rest. The exercise electrocardiogram is inconclusive because the maximal heart rate (HR) reached was only 116 beats/min. The target heart rate for this patient was 160 beats/min (85 percent of the predicted maximal rate). The thallium-201 scan shows a perfusion defect in the anteroseptal region (**arrows**) during exercise. LAO = left anterior oblique projection.

inadequate heart rate response were receiving propranolol; however, half of the patients who achieved 85 percent of the maximal predicted heart rate but whose exercise electrocardiogram was inconclusive because of resting S-T depression were also receiving propranolol (difference not significant). The limiting factors in these patients with inadequate heart rate response were leg weakness, general fatigue, shortness of breath and lack of motivation.

Role of exercise thallium-201 myocardial imaging: This procedure was extremely useful in this group of 65 patients with an inconclusive exercise electrocardiogram. Of the 20 patients with abnormal images, 19 had severe coronary artery disease (70 percent or greater narrowing of one or more major coronary arteries) as determined with arteriography. Delayed images obtained in these patients showed persistent but small defects in eight patients. Residual defects were seen in the presence or absence of wall motion abnormalities, finding in agreement with our previous study.[17]

False negative results with myocardial imaging: Of the 45 patients with normal findings on thallium-201 imaging, 37 (82 percent) had normal coronary arteriograms or less than 50 percent narrowing of one vessel. Thus, eight patients with normal exercise thallium-201 images actually had coronary artery disease. Obstruction of the coronary arteries was confined to secondary branches in six of these eight patients. Four patients with narrowing of an isolated marginal (or posterolateral) branch of the left circumflex system and two patients with significant narrowing in a marginal branch and a diagonal branch of the left anterior descending artery. It appears that exercise thallium-201 imaging is not a sensitive detector of coronary artery disease involving secondary branches. We have previously reported[18] that only 33 percent of patients with isolated coronary branch disease had abnormal results on thallium imaging, probably because of a small ischemic area that was beyond the resolution of the scintillation camera.

One of the two remaining patients with normal imaging results and coronary artery disease had triple vessel disease but extensive collateralization. In the other patient, severe narrowing was noted in the mid segment of the right coronary artery.

In the one patient with abnormal findings on exercise thallium-201 myocardial imaging and normal coronary arteriographic results, a diminutive left anterior descending artery was noted (this vessel terminated about halfway down the anterior wall of the left ventricle). On coronary angiography there was an avascular area of the myocardium near the apex, which corresponds to the region of perfusion abnormality in the exercise scan.[19]

Predictive value of exercise myocardial imaging: In our study, exercise thallium-201 scintigraphy had a specificity of 97 percent, a sensitivity of 70 percent, a predictive positive value of 95 percent and a predictive negative value of 82 percent. With this technique, we were able to predict the correct diagnosis in 56 (86 percent) of the 65 patients with an inconclusive exercise electrocardiogram. In such patients exercise thallium-201 imaging appears to be more reliable when the images are abnormal than when they are normal. This conclusion is based on the higher specificity of the test in comparison with its sensitivity. Our results also suggest that the sensitivity and specificity of exercise imaging are similar in patients with a conclusive and an inconclusive exercise electrocardiogram. This finding is in agreement with the results of McCarthy et al.[7] and

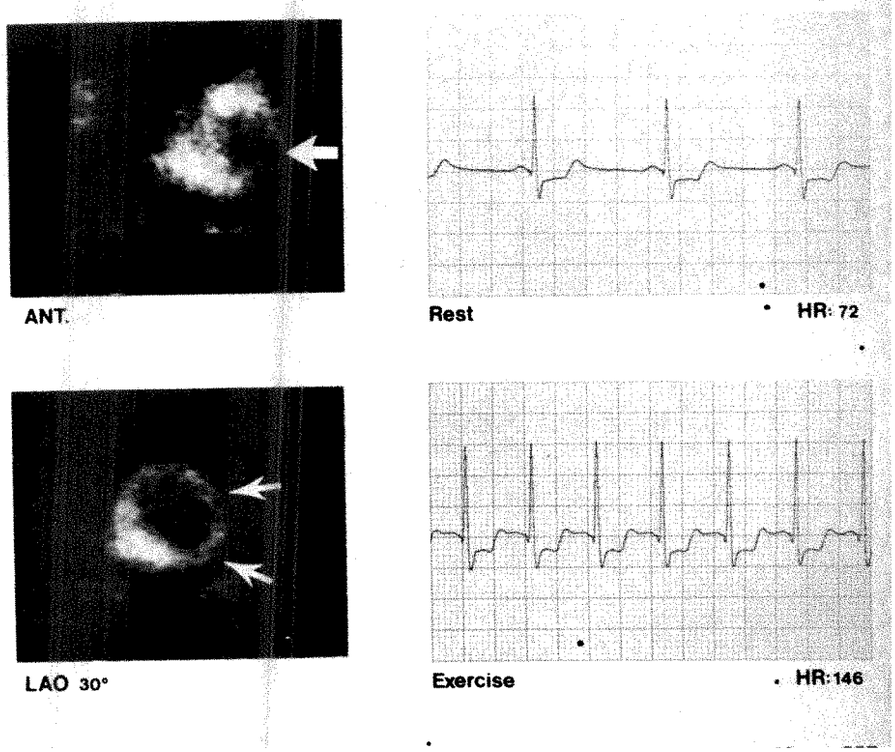


FIGURE 3. Electrocardiograms at rest and during exercise and stress myocardial thallium-201 perfusion scans in a 53 year old man with chest pain and three vessel coronary artery disease. Electrocardiographic lead V_5 shows S-T depression at rest. The exercise electrocardiogram is inconclusive because of the absence of additional 2 mm S-T depression. Myocardial uptake of thallium-201 at peak treadmill stress shows abnormal perfusion in the anterior (ANT) and left anterior oblique (LAO) projections (**arrows**). HR = heart rate (beats/min).

is of interest: Fifty-four percent of the exercise electrocardiograms in our study were inconclusive because only a submaximal work load had been performed.

Our results are important in light of a previous study by McLaughlin et al.,[20] who evaluated 12 patients with coronary artery disease at two levels of exercise. They found that only 16 (53 percent) of 30 ischemic defects present at maximal exercise were evident during light exercise. However, it is not clear from their study how many patients (rather than ischemic defects) did not manifest any ischemic defects on light exercise. Moreover, during experimental production of myocardial ischemia, the electrocardiographic abnormalities appear later than the perfusion, metabolic and wall motion abnormalities. This fact, in combination with variations in the level of "light" exercise, may explain why 12 of our 16 patients with coronary artery disease showed scintigraphic abnormalities during submaximal exercise in the absence of ischemic S-T changes. We concluded, therefore, that light exercise is more likely to underestimate the extent of myocardial ischemia than to detect ischemia.

Although all of our 19 patients with no coronary artery disease had normal exercise images at a submaximal heart rate, we still suggest caution in accepting a negative exercise scan at a suboptimal heart rate as clear evidence of the absence of myocardial ischemia. Further studies are needed to confirm our findings.

The relatively low sensitivity of exercise thallium-201 imaging in this selected population may be related in part to the inclusion of patients with disease in coronary arterial branches. In a previous study,[17] we found that exercise thallium-201 imaging has a sensitivity of 88 percent in patients with 70 percent or greater narrowing of the major coronary vessels. McCarthy et al.[7] also found that exercise thallium-201 imaging is useful in patients with inconclusive exercise electrocardiograms and that the values for sensitivity and specificity of exercise imaging are not statistically different from those of treadmill exercise testing if only the conclusive (positive or negative) results are analyzed. Our experience (unpublished data) supports this conclusion.

Clinical Implications

We believe that thallium-201 imaging is valuable in screening patients with an inconclusive exercise electrocardiogram for coronary heart disease. The high specificity and predictive accuracy of this noninvasive method could reduce the need for coronary arteriography in such patients.

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Pathogenesis of Paroxysmal Hypertension Developing During and After Coronary Bypass Surgery: A Study of Hemodynamic and Humoral Factors

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A prospective study of hypertension first appearing during and after saphenous vein bypass coronary surgery was performed in 28 patients to examine the incidence, hemodynamics and mechanism of this problem. In 15 patients (54 percent) new hypertension developed (mean arterial pressure greater than 107 mm Hg), characterized by increased peripheral vascular resistance and unchanged cardiac output within 1 hour after surgery. These 15 patients had a longer history of angina of greater severity, but also had relatively well preserved ventricular myocardium. Because plasma renin activity was depressed in patients in the hypertensive group, activation of the renin-angiotensin system was not important in the pathogenesis of this postoperative hypertension. The expected decrease in total peripheral resistance at the onset of cardiopulmonary bypass was observed in all patients, but later during bypass the peripheral resistance increased in all patients in association with a rise in plasma epinephrine levels. Patients who had hypertension postoperatively had a greater increase in arterial pressure and total peripheral resistance during cardiopulmonary bypass than did those with normal postoperative blood pressure. An elevation in plasma epinephrine and norepinephrine concentration, suggesting enhanced sympathoadrenal responsiveness to the challenge of cardiopulmonary bypass, was characteristic of the hypertensive group. This evidence of enhanced sympathetic activity during surgery may be a useful predictor of the development of postoperative hypertension.

Hypertension after coronary bypass surgery has been characterized by an increase in total peripheral resistance with normal cardiac output.[1,2] Both the renin-angiotensin system[3–5] and the sympathetic nervous system[1,2,4] can cause vasoconstriction and have been suggested as primary mediators of the postoperative increase in total peripheral resistance. The purpose of this prospective study was to establish the incidence of postoperative hypertension in patients undergoing coronary bypass surgery, to determine whether there are useful predictors of this hypertension and to examine the mechanism of postoperative hypertension in relation to hemodynamic changes, the renin-angiotensin axis and the sympathoadrenal system.

Methods

Patients: Twenty-eight patients scheduled for elective coronary bypass surgery were studied. Usual medications including propranolol and nondiuretic antihypertensive drugs were given until the day of operation. Administration of diuretic drugs was discontinued 48 hours before operation. Recognizing the large number of intraoperative and postoperative variables, we made every attempt to standardize care. The same physicians performed surgery (R.B.K.) and anesthesia (J.G.R.) in all patients.

Surgical protocol: Radial arterial and central venous pressure catheters were inserted before anesthesia. After sternotomy, right and left atrial pressures were measured with small polyvinyl catheters that were left in place for at least 12

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hours after operation. The cardiopulmonary bypass pump was primed with Normosol R® (1,000 cc) and a solution (1,000 cc) of 5 percent dextrose and 45 percent saline. Reverse saphenous vein bypass surgery was performed under moderate systemic hypothermia during a single period of hypothermic ischemic arrest on cardiopulmonary bypass.

Premedication with diazepam, morphine sulfate and scopolamine was given 1 hour before surgery. Anesthesia was induced with diazepam (0.5 mg/kg) and maintained with a mixture of 50 percent nitrous oxide and 50 percent oxygen, pancuronium (0.1 mg/kg), fentanyl (up to 10 μg/kg) and halothane (0 to 1 percent). Before cardiopulmonary bypass, the halothane dosage was adjusted to maintain the heart rate, systolic pressure and the heart rate-pressure product within 30 percent of control values. During cardiopulmonary bypass, systemic hypotension was not treated unless the mean arterial pressure was persistently less than 50 mm Hg at a pump flow of 2.2 liters/min per m^2. If mean arterial pressure increased to 100 mm Hg at 1.6 liters/min per m^2, then either flow was reduced or halothane was administered. Halothane was not routinely administered during cardiopulmonary bypass. After cardiopulmonary bypass, systolic arterial pressure of less than 80 mm Hg was treated with an intravenous bolus injection of 5 mg of ephedrine or 100 mg of calcium chloride.

Postoperative protocol: After operation, patients were monitored in the cardiac surgery intensive care unit. Respiration was assisted by an intermittent mandatory ventilation volume cycle respirator to maintain normal arterial blood gases. Patients were sedated with morphine sulfate as needed to relieve pain. Care was taken that all patients were adequately sedated and free of remediable respiratory difficulties before a diagnosis of postoperative hypertension was made. The cardiac surgery intensive care unit provided on-line computer measurement and treatment facilities[6] that allowed standardized care for all patients. Blood pressure, left and right atrial pressure, heart rate and body temperature were recorded at 5 minute intervals. Blood or albumin was administered by computer to maintain left atrial pressure at 8 mm Hg in all patients.

Plasma renin activity and catecholamines: Samples of blood for measurement of plasma renin activity, epinephrine, norepinephrine, arterial blood gases, hemoglobin, sodium and potassium were taken (1) before induction of anesthesia, (2) immediately after sternotomy, (3) 5 minutes after the start of cardiopulmonary bypass, (4) before release of the aortic cross clamp near termination of cardiopulmonary bypass, (5) at the time of closure of the sternum, and (6) 1 hour after the patient's arrival in the cardiac surgery intensive care unit, when the first measurement of cardiac index was obtained. Plasma renin activity was measured in all patients with radioimmunoassay techniques,[7] and plasma epinephrine and norepinephrine were measured in the last 21 patients with a modification of the radioenzymatic method of Passon and Peuler.[8]

Hypertension: Hypertensive patients were defined as those in whom a mean arterial pressure greater than 107 mm Hg developed in the cardiac surgery intensive care unit. Patients were observed during the 1st hour without antihypertensive intervention unless blood pressure exceeded 175/110 mm Hg. After 1 hour in the unit, or before antihypertensive therapy was begun, a cardiac index was measured in duplicate using the green dye-dilution technique, with dye flowing from the left atrium to the radial artery.

Statistical analyses: Analyses comparing the hypertensive and nonhypertensive patients at specific time periods were performed using Student's t test and data are reported as mean ± standard error of the mean. Discriminant analysis and linear regression techniques[9] were used to evaluate the predictive value of the following preoperative variables in relation to postoperative hypertension: history of hypertension, use of antihypertensive medication, propranolol therapy, severity of angina (Canadian Heart Association classification), duration of angina, number of saphenous vein bypass grafts inserted, number of previous myocardial infarctions and presence of a normal left ventriculogram. Left ventricular function was evaluated by at least single plane angiography in all patients. Correlation coefficients were determined for mean arterial pressure versus plasma epinephrine, norepinephrine and renin activity.

Results

Fifteen (54 percent) of the 28 patients had a mean arterial pressure greater than 107 mm Hg during the 1st hour in the cardiac surgery intensive care unit, and another patient became hypertensive shortly thereafter. Four of these patients were severely hypertensive (mean arterial pressure greater than 130 mm Hg) soon after arriving in the unit. No patient became hypertensive while in the operating room after cardiopulmonary bypass.

Preoperative measurements: Analysis of preoperative data revealed no significant differences between the postoperatively hypertensive and nonhypertensive patients with regard to age, sex, body surface area or history of myocardial infarction, diabetes mellitus and hypertension (Table I). Preoperative treatments, including administration of antihypertensive medications and propranolol, were similar in the two groups. Patients who became hypertensive postoperatively tended to have a history of more severe angina (class III or IV) than those who were nonhypertensive (11 of 15 versus 3 of 13 patients, $p < 0.06$). Hypertensive patients also tended to have a longer mean duration of angina than those in the nonhypertensive group (45 ± 16 versus 21 ± 7 months), although this difference was not statistically significant.

Normal left ventriculograms were more common in patients in the hypertensive group (9 of 15 versus 3 of 13 patients, $p < 0.05$). The three patients who had significant (greater than 50 percent) left main coronary arterial stenosis were hypertensive postoperatively. Left

TABLE I

Preoperative Clinical Characteristics

	Nonhypertensive Patients	Hypertensive Patients	p Value
Age (yr)	54 ± 2	58 ± 2	NS
BSA (m^2)	1.96 ± 0.07	1.96 ± 0.05	NS
Angina			
Duration (mo)	21 ± 7	45 ± 16	NS
Class III or IV (n)	3 of 13	11 of 15	<0.06
Normal left ventriculogram (n)	3 of 13	9 of 15	<0.05
Propranolol therapy (n)	6 of 13	10 of 15	NS
History of hypertension (n)	2 of 13	6 of 15	NS
History of myocardial infarction (n)	9 of 13	7 of 15	NS

BSA = body surface area; n = number of patients; NS = not significant; p = probability.

anterior descending coronary arterial stenosis was present in every patient. There was no difference between the two groups regarding single, double or triple vessel disease. In particular, stenoses in the proximal portions of the left anterior descending and the left circumflex arteries occurred in both nonhypertensive and hypertensive patients with equal frequency.

Of all the preoperative factors analyzed, four proved of most value in predicting which patients would have postoperative hypertension: the severity of angina, the duration of angina, the number of saphenous vein bypass grafts and the presence of a normal left ventriculogram. The discriminant function based on these four variables yielded two false positive and two false negative results for a specificity of 83 percent and a sensitivity of 88 percent.

Intraoperative hemodynamic measurements: Before cardiopulmonary bypass, systemic arterial blood pressure was labile. Peak systolic blood pressure occurred with endotracheal intubation; 16 patients had a systolic pressure greater than 160 mm Hg for brief periods (less than 5 minutes). This pressure usually responded to an increased dose of halothane. Hypertension with intubation was not predictive of postoperative hypertension; 7 of 16 patients who had hypertension during endotracheal intubation were not hypertensive postoperatively.

Cardiopulmonary bypass was associated with a profound decrease in systemic arterial pressure in all patients (Fig. 1). Five minutes after the onset of cardiopulmonary bypass, mean arterial pressure and total peripheral resistance were significantly greater in patients who had postoperative hypertension (Fig. 1, Table II). During cardiopulmonary bypass, mean arterial pressure and total peripheral resistance increased in all patients, but to significantly higher levels in the patients with postoperative hypertension ($p < 0.001$). The hypertensive patients had more grafts (four and five saphenous vein grafts) as well as slightly longer aortic cross-clamp and cardiopulmonary bypass times (Table II). Independently, there was no significant correlation between postoperative hypertension and either aortic cross-clamp time or total cardiopulmonary bypass time. The degree of hemodilution (hemoglobin 8.2 g/100 ml) and systemic hypothermia (30 to 31° C) during bypass was similar in both study groups. Immediately after discontinuation of cardiopulmonary bypass, systolic blood pressure increased to greater than 90 mm Hg in all but six patients, who were treated with either an intravenous bolus injection of ephedrine (5 mg) or calcium chloride (0.5 mg/kg). Further supportive measures were not required, and all patients remained normotensive for the duration of the operation.

Immediately before leaving the operating room, the patients with postoperative hypertension had a significantly higher blood pressure level (hypertensive group 119/67 mm Hg, mean 86 versus nonhypertensive group 106/59 mm Hg, mean 76; $p < 0.05$). Right and left atrial pressures, urinary output, amount of crystalloid solution infused, hemoglobin and arterial blood gases were not significantly different in the two groups.

Postoperative hemodynamic measurements: Mean arterial pressures in the two groups were significantly different on the patients' arrival in the cardiac surgery intensive care unit (Fig. 1). Four patients had marked systolic hypertension (greater than 175 mm Hg) soon after arrival in the recovery room, and treatment was initiated immediately after measurement of cardiac index.

Nonhypertensive and hypertensive patients had similar cardiac indexes and stroke volumes but markedly different total peripheral vascular resistances ($p < 0.001$) (Table III). Right and left atrial pressures, temperature (34° C), hemoglobin (12 g/100 ml) and

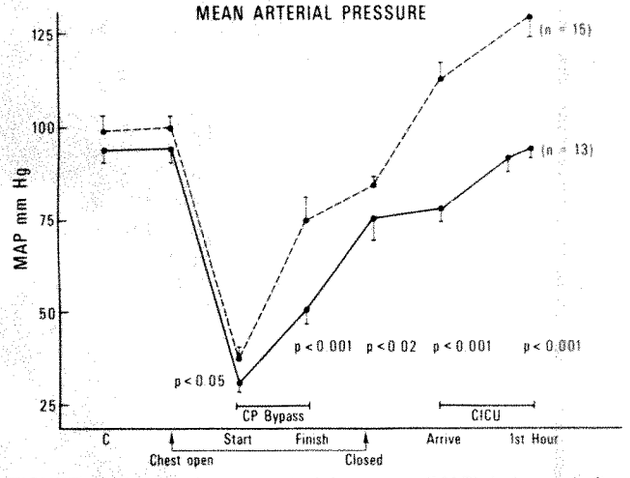


FIGURE 1. Changes in mean arterial pressure (MAP) during and after saphenous vein bypass surgery in patients with (**broken line**) and without (**unbroken line**) postoperative hypertension. C = control values before anesthesia; CICU = cardiac surgery intensive care unit; CP = cardiopulmonary; Finish = before release of aortic cross clamp immediately before discontinuation of cardiopulmonary bypass; n = number; p = probability; Start = 5 minutes after start of cardiopulmonary bypass.

TABLE II

Intraoperative Hemodynamics

	Nonhypertensive Patients	Hypertensive Patients	p Value
Bypass time (min)	57 ± 2	68 ± 5	<0.07
Cross-clamp time (min)	30 ± 9	37 ± 3	<0.10
Bypass grafts			
Average (n)	2.8 ± 0.2	3.5 ± 0.3	<0.05
4–5 Grafts (number of patients)	2 of 13	9 of 15	<0.02
MAP (mm Hg)			
Start*	30 ± 2	38 ± 3	<0.05
Finish†	51 ± 4	75 ± 6	<0.001
TPR (units · m^2)			
Start*	15 ± 1	19 ± 1	<0.05
Finish†	27 ± 2	40 ± 3	<0.001

Bypass time = duration of cardiopulmonary bypass; bypass grafts = saphenous vein bypass grafts; cross-clamp time = duration of aortic cross clamping during cardiopulmonary bypass. MAP = mean arterial pressure; p = probability; TPR = total peripheral resistance = MAP/(bypass pump flow/m^2).

* Start (5 minutes after onset of cardiopulmonary bypass); † finish (immediately before release of aortic cross clamp).

TABLE III

Postoperative Hemodynamics

	Nonhypertensive Patients	Hypertensive Patients	p Value
MAP (mm Hg)	95 ± 2 (135/72)	127 ± 3 (167/97)	<0.001
CI (liters/min per m^2)	2.38 ± 0.12	2.47 ± 0.15	NS
SV (cc/min)	53 ± 4	52 ± 4	NS
LAP (mm Hg)	7.7 ± 0.4	9.7 ± 1.5	NS
TPR (units · m^2)	37 ± 2	51 ± 3	<0.001

CI = cardiac index; LAP = left atrial pressure; MAP = mean arterial pressure; NS = not significant; p = probability; SV = stroke volume; TPR = total peripheral resistance = (MAP − right atrial pressure)/CI.

arterial blood gases were similar in the two groups. Atrial pacing was routinely initiated in any patient with a spontaneous sinus rate of less than 80 beats/min. Therefore, analysis of spontaneous heart rate could not be meaningfully performed.

Hypertensive patients were all treated successfully with intravenous nitroprusside by computer[10] to maintain mean arterial pressure at 100 mm Hg. The mean duration of therapy was 6 hours, although one patient also required continued antihypertensive medication on the 1st postoperative day. All patients were normotensive without medication for the remainder of their hospitalization. Postoperative enzyme determinations and electrocardiograms did not identify a postoperative myocardial infarction in any patient (serum glutamic oxaloacetic transaminase on postoperative day 1: nonhypertensive patients 53 ± 6 versus hypertensive patients 59 ± 6 IU/liter; difference not significant).

Plasma renin activity and catecholamines: Serial determinations of plasma renin activity revealed that patients who remained normotensive after operation tended to have higher levels throughout the study than did those who had hypertension, but this difference was not statistically significant (Fig. 2). Plasma renin activity increased at the onset of cardiopulmonary bypass in both groups, but this change was statistically significant only in the nonhypertensive group ($p < 0.01$). Plasma renin activity changed very little during cardiopulmonary bypass in most patients, despite the very decreased and nonpulsatile arterial pressure. After cardiopulmonary bypass, plasma renin activity decreased significantly in both groups ($p < 0.05$) and approached prebypass levels.

Plasma epinephrine levels were similar in the periods before cardiopulmonary bypass in both groups of patients (Fig. 3). With the onset of cardiopulmonary bypass, plasma epinephrine increased in both groups, but to a higher level in the hypertensive patients. During bypass, plasma epinephrine levels continued to rise. This was most strikingly observed in one patient whose bypass time was prolonged and whose epinephrine level reached 5,736 pg/ml. After cardiopulmonary bypass, plasma epinephrine levels decreased. After the patients had spent 1 hour in the cardiac surgery intensive care unit, plasma epinephrine levels were significantly higher ($p < 0.001$) than control values before cardiopulmonary bypass in the hypertensive group only. There was no significant difference between plasma epinephrine levels in the two groups at that time.

Plasma norepinephrine levels were significantly different in nonhypertensive and hypertensive groups both during cardiopulmonary bypass and in the cardiac surgery intensive care unit (Fig. 4). Before cardiopulmonary bypass, the two groups had similar levels of plasma norepinephrine. In hypertensive patients, plasma norepinephrine increased ($p < 0.01$) within 5 minutes of onset of cardiopulmonary bypass, whereas there was little change in the nonhypertensive patients. During cardiopulmonary bypass, plasma norepineph-

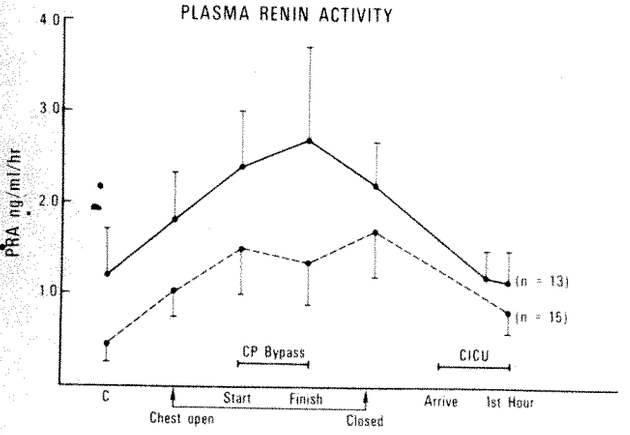


FIGURE 2. Changes in plasma renin activity (PRA) during and after saphenous vein bypass surgery in patients with and without postoperative hypertension. Symbols and abbreviations as in Figure 1.

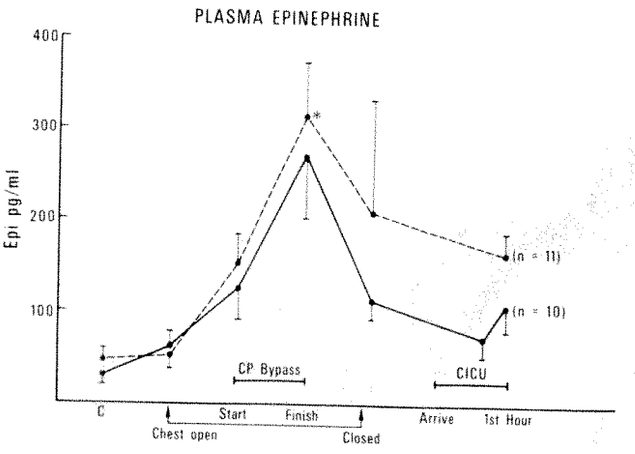


FIGURE 3. Changes in plasma epinephrine (EPi) during and after saphenous vein bypass surgery in patients with and without postoperative hypertension. One patient is excluded (see text). Symbols and abbreviations as in Figure 1.

rine levels decreased or remained unchanged in most patients. Two patients who had postoperative hypertension had a prolonged bypass time and had striking increases in plasma norepinephrine (2,181 and 1,040 pg/ml, respectively) during the bypass period. These patients were excluded from statistical analysis because technical difficulties necessitated the administration of drugs not included in the protocol. At the finish of cardiopulmonary bypass, there was a positive correlation of plasma norepinephrine levels with mean arterial pressure ($r = 0.47$, $p < 0.05$) and of plasma norepinephrine levels with systemic vascular resistance ($r = 0.52$, $p < 0.03$) in all patients studied. After 1 hour in the intensive care unit, plasma norepinephrine in normotensive patients decreased slightly and in hypertensive patients increased by approximately 50 percent, attaining levels higher than control values before cardiopulmonary bypass ($p < 0.01$) and significantly higher than simultaneous levels in the normotensive group ($p < 0.01$). At this time, there was a positive correlation between mean arterial blood pressure and both plasma epinephrine ($r = 0.59$, $p < 0.01$; Fig. 5) and norepinephrine ($r = 0.58$, $p < 0.01$; Fig. 6). There was no correlation between plasma renin and blood pressure.

Discussion

Hypertension developed in more than 50 percent of our patients within 1 hour after saphenous vein bypass surgery. The incidence and time of onset of this hypertension are consistent with previous reports.[1,2,4,11,12] Hemodynamic studies confirmed that both systolic and diastolic blood pressures were increased in these patients. Cardiac index remained unchanged and therefore calculated total peripheral resistance was increased. Circulating epinephrine and norepinephrine levels were elevated in the hypertensive patients, suggesting enhanced activity of the sympathetic nervous system. Postoperative hypertension required treatment for only a few hours after surgery, and most patients remained normotensive thereafter.

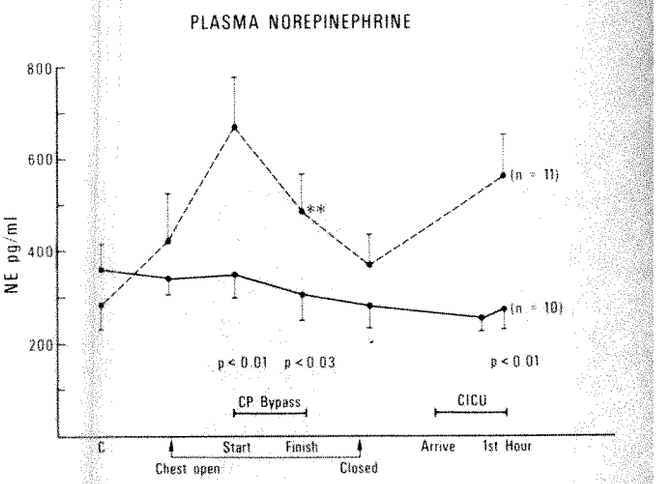


FIGURE 4. Changes in plasma norepinephrine (NE) during and after saphenous vein bypass surgery in patients with and without postoperative hypertension. One patient is excluded (see text). Symbols and abbreviations as in Figure 1.

Preoperative predictive factors: Four factors appeared to be useful in predicting which patients were more likely to have hypertension in the period immediately after coronary bypass surgery: the severity of preoperative angina and its duration, the number of saphenous vein grafts needed and the presence of a normal left ventriculogram. Our observations suggest that patients with severe angina of prolonged duration but with well preserved ventricular myocardium and coronary anatomy suitable for multiple (more than three) saphenous vein bypass grafts tend to become hypertensive postoperatively. We did not find that preoperative hypertension correlated with postopera-

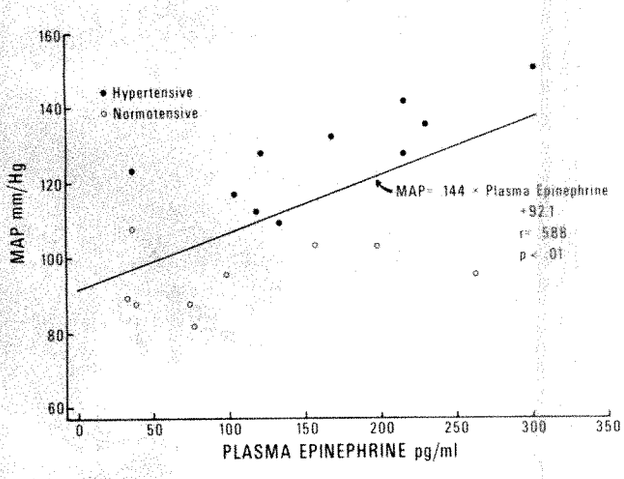


FIGURE 5. Regression analysis comparing mean arterial pressure (MAP) with plasma epinephrine concentration for all patients studied after 1 hour in the intensive care unit. p = probability; r = correlation coefficient.

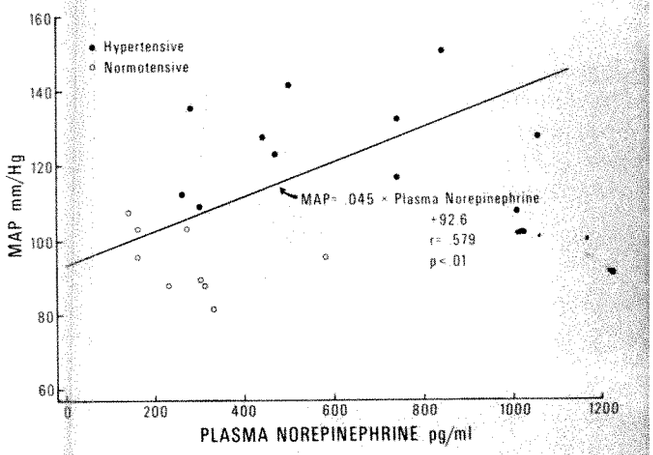


FIGURE 6. Regression analysis comparing mean arterial pressure (MAP) with plasma norepinephrine concentration for all patients studied after 1 hour in the intensive care unit. Abbreviations as in Figure 5.

tive elevation of blood pressure, and this observation is consistent with a previous report.[11] Although other investigators[4] linked preoperative hypertension, particularly when associated with left main coronary artery disease, with an increased incidence of postoperative hypertension, they found no correlation between the latter and severity of angina, left ventricular contraction abnormalities or the number of coronary arterial bypass grafts.

Relation between hemodynamic and humoral factors: The relation between the hemodynamic and humoral changes observed during cardiopulmonary bypass and the emergence of hypertension after saphenous vein bypass surgery is not well defined. Our study demonstrates that patients who have hypertension after saphenous vein bypass surgery respond to cardiopulmonary bypass differently from nonhypertensive patients. A sharp decrease in systemic arterial blood pressure with the onset of cardiopulmonary bypass is expected[13] and occurred in all of our patients. However, the patients who had hypertension postoperatively had higher values for mean arterial pressure and total peripheral resistance than did the nonhypertensive group at the onset of cardiopulmonary bypass. After 5 minutes of bypass, patients who subsequently had postoperative hypertension had an elevated plasma norepinephrine level, whereas in normotensive patients the plasma norepinephrine level was unchanged. In contrast, plasma epinephrine increased to a similar extent with the onset of cardiopulmonary bypass in both hypertensive and nonhypertensive patients. The data suggest increased sympathoadrenal responsiveness to the challenge of cardiopulmonary bypass in the hypertensive group. This index of enhanced sympathetic activity in the hypertensive group may provide a prognostic sign for the development of postoperative hypertension.

Role of plasma renin activity and activation of renin-angiotensin system: A modest increase in plasma renin activity was observed in both hypertensive and nonhypertensive patients after 5 minutes on cardiopulmonary bypass. There was little change in renin levels in either group during the subsequent course of bypass. This finding and the observation that plasma renin activity was greater in nonhypertensive than in hypertensive patients throughout the study are not compatible with the notion that the increased total peripheral resistance observed during cardiopulmonary bypass in patients with postoperative hypertension might be due to activation of the renin-angiotensin system. In addition, there was no correlation between postoperative blood pressure and plasma renin levels. These data do not permit us to relate postoperative hypertension to enhanced activity of the renin-angiotensin system. Other investigators have reported that plasma renin activity decreased[14] or that angiotensin II was increased[3] at the onset of cardiopulmonary bypass. Comparison between our study and these reports is difficult because of differences in cardiac diagnosis of the patients, variable use of hypothermia and normothermia with cardiopulmonary bypass and major differences in anesthetic technique, including premedication with large dose steroids. Previous studies[3–5] further suggested that the renin-angiotensin system is an important mediator of the increased vascular resistance observed in patients with postoperative hypertension. The apparent inconsistency between these studies and our study may be related to their inclusion of patients with valvular heart disease, whose volume status[15] and hemodynamic performance may be different from those of patients with ischemic heart disease. Volume repletion by a computer-controlled system in our study may also have contributed to the absence of higher postoperative renin levels.

Plasma norepinephrine levels and activation of the sympathetic nervous system: The finding that plasma norepinephrine levels were increased significantly after operation in the hypertensive but not in the nonhypertensive patients suggests that the sympathetic nervous system may be a mediator of postoperative hypertension. Plasma epinephrine levels tended to be higher in hypertensive than in nonhypertensive patients after operation, but the difference between groups was not statistically significant. Only in the hypertensive group were plasma epinephrine levels significantly elevated above the levels before cardiopulmonary bypass. However, the postoperative mean arterial pressure correlated with both plasma norepinephrine and epinephrine levels. These findings confirm the observations of Roberts et al.[4] and Fouad et al.,[12] who previously suggested that the hypertension that follows coronary bypass surgery may be related to activation of the sympathetic nervous system.

Role and mechanism of increased sympathetic activity: The pathophysiologic mechanism of increased sympathetic activity in patients who have hypertension after saphenous vein bypass surgery is uncertain. The cardiogenic hypertensive chemoreflex described by James et al.[16] offers the attractive hypothesis that platelet aggregates on coronary atherosclerotic plaques in the proximal left coronary arterial system could release serotonin and trigger a hypertensive response. However, analysis of coronary arteriograms in our study revealed no differences in the incidence of proximal left coronary disease in the hypertensive and nonhypertensive patients. Spinal sympathetic reflexes arising from coronary arterial receptors as demonstrated by Brown and Malliani[17] provide an alternative hypothesis. Chronic hypovolemia associated with ischemic heart disease[15,18] may link the vasomotor instability and increased sympathetic nerve activity observed in postoperatively hypertensive patients. Our study suggests that increases in catecholamines and total peripheral resistance during cardiopulmonary bypass presage similar postoperative responses in the hypertensive group. This increased sympathetic response may be more common in patients with severe, long-standing angina and well preserved left ventricular function. The pathophysiologic role of the sympathetic nervous system in the control of blood pressure during and after saphenous vein bypass surgery deserves further investigation.

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Early Results With Composite Strut Caged Ball Prostheses

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The Starr-Edwards model 6400/10 mitral and 2400/10 aortic valve prostheses incorporate metallic tracks on the inner aspects of cloth-covered struts in an attempt to preserve the favorable thromboembolic performance of cloth-covered valves while avoiding the risk of cloth wear. Two hundred seventy operative survivors of mitral valve replacement with the model 6400/10 prosthesis, all on continuous anticoagulant therapy, have been followed up for a mean period of 2.3 (maximal 6) years. The late survival rate is 91 percent and the removal-free rate is 94 percent at 5 years. The rate of embolism (mean ± standard error of the mean) is 4.6 ± 0.9 percent per patient-year. Significant bleeding complications occurred at a rate of 1.0 ± 0.2 percent per patient-year; there were no deaths.

Two hundred forty operative survivors of aortic valve replacement with a model 2400/10 prosthesis, all on continuous anticoagulant therapy, have been followed up for a mean of 2.0 (maximal 7) years. The 5 year survival rate is 84 percent and the removal-free rate is 98 percent. Embolism occurred at a rate of 3.3 ± 0.8 percent per patient-year. Hemorrhagic complications occurred at a rate of 2.1 ± 0.6 percent per patient-year; there were three fatalities.

Cloth wear and hemolysis have not been significant problems with this prosthesis, and the rates of thromboembolism are comparable with those reported for xenograft bioprostheses. The composite strut (track) valve prosthesis is a durable alternative to tissue valves in patients who are able to tolerate anticoagulant therapy.

The Starr-Edwards model 6400/10 mitral (Fig. 1) and 2400/10 aortic (Fig. 2) valve prostheses, introduced in 1972, are the most recent additions to a series of caged ball prostheses that date to the earliest days of cardiac valve replacement. They represent an attempt to preserve the favorable thromboembolic performance of cloth-covered valves while avoiding the risk of cloth wear. This report reviews our experience with these prostheses since 1972.

Methods

Patients: From April 1972 to October 1979, a total of 282 model 6400/10 mitral valve prostheses and 350 model 2400/10 aortic valve prostheses were implanted at the University or Oregon Health Sciences Center, Portland, Oregon; the Tucson Medical Center, Tucson, Arizona; and Mercy Hospital, San Diego, California. These prostheses incorporate metallic tracks on the inner aspects of their cloth-covered struts. The ball is composed of hollow Stellite®. In the current configuration, the orifice cloth is a lock-stitch run-resistant Dacron® fabric protected by metallic studs to eliminate the potential for orifice cloth wear.

The clinical characteristics of the patients discharged on anticoagulant therapy are listed in Table I. All patients underwent replacement of a single valve, although other concomitant procedures were common. Since 1974, valve selection has primarily been based on size, the track valve being reserved for patients with a larger valve orifice (equal to or greater than 30 mm mitral or 25 mm aortic). Before 1978, most replacements were accomplished using cardiopulmonary bypass with moderate systemic hypothermia (30° C), supplemented

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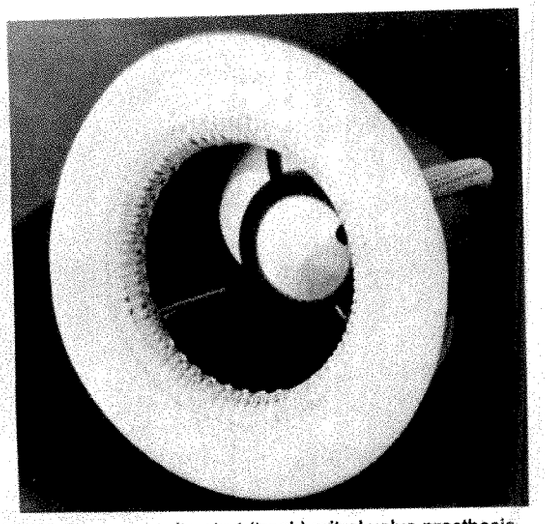


FIGURE 1. The composite strut (track) mitral valve prosthesis.

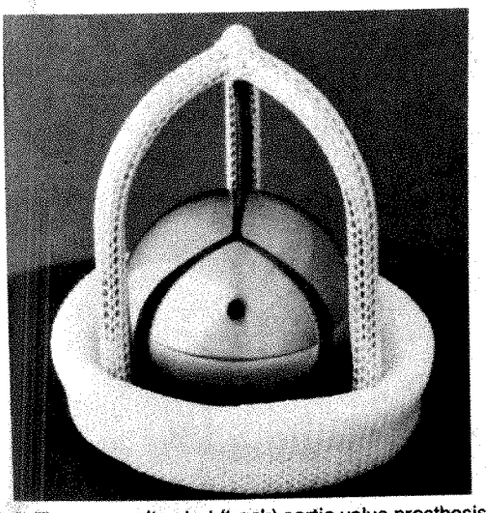


FIGURE 2. The composite strut (track) aortic valve prosthesis.

with continuous coronary perfusion for aortic valve replacement. Recently, systemic hypothermia (30° C) with cold potassium cardioplegia (4° C) has been used.

Follow-up: The patients were followed up with yearly questionnaires; telephone contact was used when questionnaires were not returned or when a complication was suspected. Seventy-four percent of patients with model 6400/10 and 84 percent of patients with model 2400/10 were accounted for during the 18 month period ending in October 1979, reflecting in part a highly mobile patient population from three disparate medical centers. The actuarial method was used to compute survival and embolism-free curves.[1]

Results

Aortic valve replacement: Twenty-three (7 percent) of 350 patients died from events causally or temporally (less than 30 days) related to valve replacement with the model 2400/10 aortic prosthesis. Two hundred forty patients were discharged on continuous anticoagulant therapy. Four of 25 late deaths (16 percent) were valve-related (Table II). The survival rate at 5 years (mean ± standard error of the mean) is 84 ± 3.3 percent (Fig. 3).

TABLE I

Clinical Features of Patients Undergoing Valve Replacement With the Track Valve Prosthesis

	Aortic	Mitral
Operative survivors (n)	240	270
Male/female ratio	6:1	2:3
Mean age (yr)	57.8	54.6
Mean valve size (mm)	25	30
Associated procedures (%)		
Aortocoronary bypass	33	15
Valve reparative	2	9
Total follow-up (patient-yr)	515	613
Follow-up (yr)		
Mean	2.0	2.3
Maximal	7	6

Five aortic valve prostheses required replacement during the follow-up period, all during the 1st year. Three prostheses were removed for prosthetic infection and two for perivalvular leak. The removal-free rate was 98 ± 1 percent at 5 years.

There were 17 instances of embolism (3 fatal, 10 with residual neurologic deficit, 4 transient) in 14 patients. The rates of embolism were 3.3 ±0.8 percent per patient-year for all emboli and 2.5 ± 0.7 percent per patient-year for serious emboli (Fig. 4). Hemorrhagic complications (gastrointestinal, cerebral or hemarthrosis) occurred at a rate of 2.1 ± 0.6 percent per patient-year; there were three deaths.

Mitral valve replacement: Twelve (4 percent) of 282 patients undergoing mitral valve replacement died from events causally or temporally (less than 30 days) related to surgery. One (7 percent) of 15 late deaths was valve-related (Table II). The late survival rate at 5 years is 91 ± 3 percent (Fig. 3).

Four mitral valve prostheses required replacement, two for prosthetic infection, one for thrombotic stenosis and one for recurrent embolism. The removal-free rate at 5 years is 94 ± 3 percent.

There were 28 thromboembolic events (none fatal, 13 residual, 15 transient) in 26 patients for a rate of embolism of 4.6 ± 0.9 percent per patient-year for all emboli and 2.1 ± 0.6 percent per patient-year for serious

TABLE II

Causes of Late Death in Patients With a Track Valve Prosthesis

	Aortic	Mitral
Valve-related	4 (16%)	1 (7%)
Cardiac	5 (20%)	7 (47%)
Cardiac	5 (20%)	7 (47%)
Noncardiac	4 (16%)	6 (40%)
Unknown	12 (48%)	1 (7%)
Total	25	15

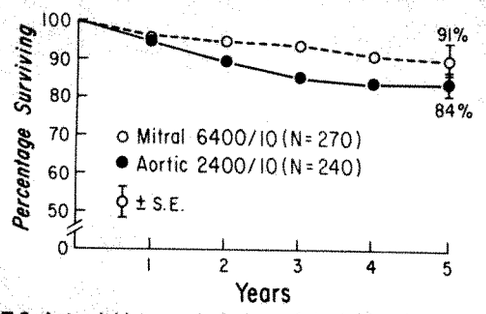


FIGURE 3. Actuarial late survival curves for mitral and aortic composite strut prostheses; operative survivors only. N = number; S.E. = standard error of the mean.

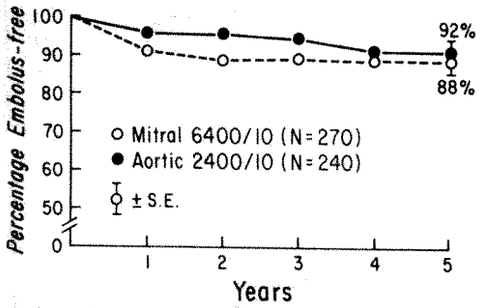


FIGURE 4. Actuarial embolus-free curves for mitral and aortic composite strut prostheses; operative survivors only.

emboli. The actuarial embolus-free rate at 5 years is 88 ± 2 percent (Fig. 4). All patients were on continuous anticoagulant therapy. Significant bleeding complications occurred at a rate of 1.0 ± 0.2 percent per patient-year; there were no deaths.

Discussion

The first clinically successful cardiac valve prostheses were of caged ball design. The efficacy and durability of these prostheses have been documented up to 15 years after implantation.[2] The major drawback to these and all other valve prostheses developed to date has been the formation of thrombus on the valve, with a significant incidence of peripheral embolization. Modifications of the original ball valve prosthesis, as well as the introduction of other prostheses of different design, have not been totally successful in eliminating the problem. The introduction of cloth covering of the orifice and struts effected a significant decrease in the incidence of thromboembolism.[3,4] However, cloth tear leading to hemolysis or embolism dampened enthusiasm for this innovation, particularly when the prosthesis was in the aortic position where the cloth was subjected to greater shear forces.

Role of anticoagulant therapy: The Starr-Edwards composite strut (track) prostheses were designed to retain the proved effectiveness and durability of the caged ball prosthesis while minimizing problems related to thromboembolism and cloth wear. We had initially hoped that this design modification would also eliminate the necessity for continuous anticoagulant therapy. However, this latter goal was not realized, because it soon became obvious that patients who did not receive anticoagulant therapy experienced greater morbidity and mortality.[5] We therefore recommend that all patients with ball valve prostheses, regardless of design, receive continuous anticoagulant therapy in the absence of an overriding contraindication. Anticoagulation can be stopped with low risk for brief periods of time in the event of major trauma or surgery.

Incidence of thromboembolism: Has the composite strut prosthesis maintained the thromboembolic protection of cloth covering while eliminating the risk of cloth wear? Embolus-free curves of patients undergoing mitral and aortic valve replacement at this institution with totally cloth-covered (models 6310/20 and 2310/20) and composite strut valve prostheses are presented in Figures 5 and 6. Although occupying different time frames, the groups are roughly comparable in major clinical variables. From these data, it can be seen that the rate of embolism with the track valve prosthesis is nearly identical to that of the totally cloth-covered prosthesis. Moreover, hemolysis and cloth wear have not been a problem to date with the track valve.

Role of track valve prosthesis versus xenograft valve: What should be the current role of the track valve prosthesis? Randomized studies of current cardiac prostheses have not been performed, and the hazards of interinstitutional comparisons are well known. These include differences in patient populations and patient selection and nonuniform long-term postoperative management of anticoagulant therapy by a variety of

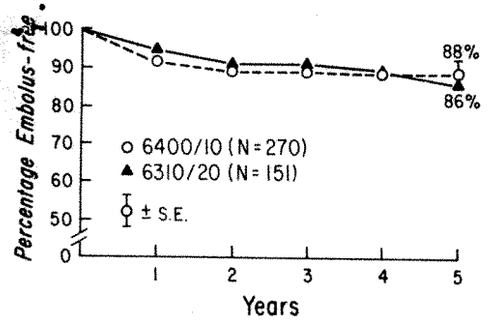


FIGURE 5. Actuarial embolus-free curves for two models of mitral ball valve prosthesis.

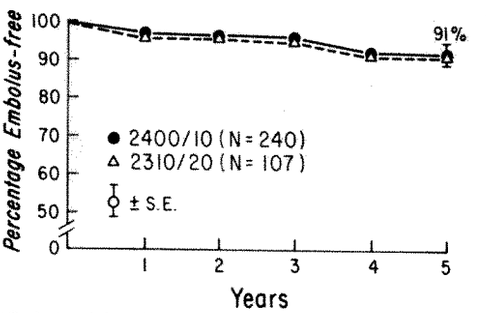


FIGURE 6. Actuarial embolus-free curves for two models of aortic ball valve prosthesis.

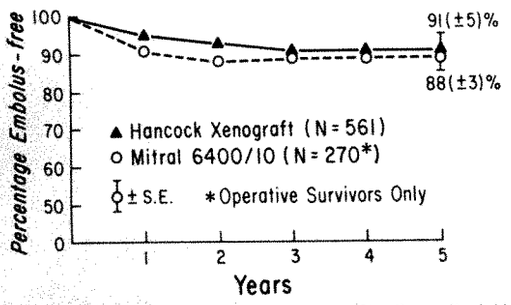


FIGURE 7. Actuarial embolus-free curves for the mitral Hancock xenograft and the composite strut valves.

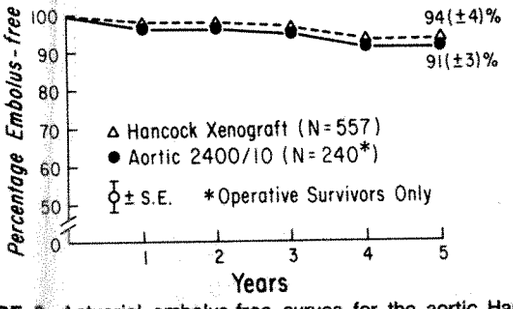


FIGURE 8. Actuarial embolus-free curves for the aortic Hancock xenograft and the composite strut valves.

clinicians. However, comparison with the data of Oyer et al.[6] at Stanford, who used Hancock porcine xenografts exclusively in a clinically comparable group of patients during the same period of time, shows no significant difference in thromboembolic performance (Fig. 7 and 8). One third of their mitral xenograft recipients received long-term anticoagulant therapy. Sudden catastrophic thrombosis in patients on anticoagulant therapy, which is a major problem with the tilting disc valve and could conceivably have accounted for sudden death of unknown cause in their series, has not been seen by us nor previously reported.

Role of valve size: In our selection of the proper valve for a particular patient, some consideration is given to valve size. Although the mean gradient across the 23 mm size valve is in the range of 20 mm Hg, higher gradients are occasionally seen, perhaps related to the accumulation of fibrin on the cloth-covered orifice. Hemodynamic studies in patients with large valves have been more uniformly satisfactory.[7] We therefore currently prefer track valves in sizes 30 mm (mitral) and 25 mm (aortic) or larger. In addition, patients who are thought unable to comply with a regimen of long-term anticoagulant therapy are not considered candidates for mechanical valves. The sound of the track valve is variable, but may be disturbing to some patients. A recent review of experience with the Silastic ball valve in the 1970's described elsewhere[8] demonstrates no significant difference in the 5 year rates of thromboembolism in comparison with other contemporary prostheses, including the track valve. Therefore, we choose the noncloth-covered valve, even in larger sizes, for patients who, in their judgment or that of the clinician, might be unduly bothered by prosthetic noise.

In summary, the composite strut valve offers satisfactory thromboembolic performance and a durable alternative to the glutaraldehyde-preserved porcine xenograft valve in patients who are able to tolerate anticoagulant therapy. We continue to use both the noncloth-covered and track prostheses.

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Genesis of Pericardial Knock in Constrictive Pericarditis

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A pericardial knock is a common finding in constrictive pericarditis. However, its origin has been uncertain. One hypothesis suggests that it is due to sudden deceleration of ventricular filling. To validate this hypothesis, left ventriculograms, phonocardiograms and external pulse recordings were obtained in seven patients with hemodynamic and pathologic findings of constrictive pericarditis and in seven normal subjects. Left ventriculographic silhouettes were digitized and left ventricular volumes were calculated by computer at 16 ms intervals. Curves of left ventricular volume versus diastolic filling time were constructed for each patient. Pericardial knock was recognized as an early high frequency sound recorded between 90 to 120 ms after the aortic closing sound and occurring at the trough of the *Y* descent of the jugular venous pressure tracing. The timing of the pericardial knock in five patients with constrictive pericarditis corresponded to a sudden and premature plateau of the diastolic left ventricular volume curve representing 85 ± 4 percent (mean ± standard deviation) of ventricular filling. The diastolic plateau was missing in two patients with constrictive pericarditis who had no pericardial knock. In these cases, the rate of ventricular filling was faster than normal in the first 20 percent of diastole.

Thus, this study related pericardial knock to an abrupt plateau in the diastolic left ventricular volume curve, supporting the view that sudden cessation of ventricular filling generates the pericardial knock of constrictive pericarditis. Two mechanisms are proposed by which the filling plateau may produce the knock, and it is postulated that both ventricles may participate in the knock phenomenon.

Since the first case of constrictive pericarditis was described by Chevers[1] of Guy's Hospital in 1842, the pathophysiologic basis of a high frequency early diastolic sound in this disease has intrigued investigators and clinicians alike.[2] This extra sound has been termed a pericardial protodiastolic sound to distinguish it from the third heart sound or protodiastolic gallop; lately it has been called the "pericardial knock." This sound usually occurs about 90 to 120 ms after the aortic component of the second heart sound, whereas the third heart sound occurs somewhat later (130 to 160 ms). Furthermore, the pericardial knock has a higher acoustic frequency and intensity than the third heart sound.[3]

It has been assumed that the knock is related to sudden cessation of diastolic ventricular filling when the expanding ventricles achieve the limits imposed by a nondistensible, thickened, fibrous or calcified pericardium. This assumption was based primarily on indirect experimental evidence, that is, radiology,[4–6] roentgenkymography,[7] apexcardiography[8] and interpretations of simultaneous right atrial and right ventricular pressure recordings and phonocardiographic studies.[9] In more recent and sophisticated studies, several investigators[10–12] constructed pressure-volume curves for patients with constrictive pericarditis and showed a steep sudden increase in pressure-volume ratios early in diastole. However, these authors did not correlate their pressure-volume findings with phonocardiographic data.

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Although these observations suggest that the knock is associated with abrupt changes in ventricular pressure or filling rate, no study has correlated objective measurements of ventricular filling with the knock, and several alternative explanations have been proposed, including the theory that the knock is equivalent to an early third sound gallop in the presence of rapid ventricular filling.[13] This study was therefore undertaken to validate further the hypothesis that a pericardial knock corresponds to a rapid and sudden deceleration of ventricular filling by the constricting pericardium.

Methods

Seven patients with proved constrictive pericarditis and seven normal subjects who had phonocardiograms, external pulse recordings and electrocardiograms taken just before routine cardiac catheterization were studied.

Noninvasive studies. Phonocardiograms, external pulse recordings and electrocardiograms were simultaneously obtained. All patients had their cardiac medications discontinued at least 12 hours before the study. Graphic recordings were obtained with a multichannel fluid-jet recorder (Mingograf 34, Elema-Schoenander, Siemans Company, Iselin, New Jersey) with the patients in the supine position in a noise-insulated room. Phonocardiograms were recorded using standard 50, 100 and 200 hertz filters, and a high impedance microphone (EMT 25C). External pulse recordings were performed using an Elema-Schoenander EMT 510C pulse recorder and a Marey transducer. This system was able to record frequencies as low as 0.2 hertz. Electrocardiographic lead II or III was simultaneously recorded for timing purposes, and all graphic tracings were inscribed on paper at 100 mm/s. Therefore, it was possible to measure accurately time intervals as short as 10 ms.

A *pericardial knock* was recognized as a high frequency diastolic sound recorded between 90 to 120 ms after the aortic closing sound, and occurring at the trough of the Y descent in the jugular venous pulse tracings.

Cardiac catheterization: This procedure was performed with the patients in the postabsorptive state after mild sedation with orally administered diazepam (5 to 10 mg). Right and left heart pressures were measured through fluid-filled catheters connected to Statham $P_{23}Db$ transducers and recorded on an Electronics for Medicine DR-8 recorder. Cardiac output was determined with the Fick method. Left ventricular cineangiography was then performed in the 30° right anterior oblique protection using a conventional 9 inch (22.8 cm) image intensifier and filmed at 60 frames/s.

TABLE I

Clinical Features of Seven Patients With Constrictive Pericarditis

	Patients (n)
Origin of pericarditis	
Postviral	4
Tuberculosis	1
Degos' disease	1
Idiopathic	1
Symptoms	
Dyspnea	7
Chest pain	3
Peripheral edema	2
Signs	
Jugular venous distension	7
Pleural effusion	5
Pericardial knock	5
Ascites	3
Pericardium on fluoroscopy	
Calcific	4
Noncalcific	3

Silhouettes of the left ventriculogram were traced from a Vangard projector (Vangard Instrument Corporation, Melville, New York) at 16 ms intervals between end-systole and end-diastole. These silhouettes included papillary muscles and trabeculations. The coordinates of these left ventricular silhouette outlines were digitized and volumes were calculated by direct integration, using a Varian 620-i minicomputer (Varian 620-i, Varian Data Machines, Irvine, California). This method divides the left ventricle into cylindrical slices, 1 mm thick, that are summed to give total volume using a modification of Simpson's rule.[14] No correction for rotation or distortion was used, but a correction factor for angiographic magnification was included in the computation. Left ventricular volumes calculated by this angiographic method were reproducible within 4 ± 1 percent in consecutive sinus beats. The left ventricular ejection fraction was also calculated by this method and has been shown to correlate well with ejection fraction calculated with nuclear angiography.[15]

Left ventricular filling volumes were expressed as percents of total filling volume (defined as end-diastolic minus end-systolic volume). The left ventricular end-diastolic silhouette was the largest silhouette preceding the onset of contraction (mitral valve closure). The left ventricular end-systolic silhouette was the smallest silhouette during contraction; this usually coincided with aortic valve closure. Left ventricular diastole was defined as the time from the smallest to the largest left ventricular cavity size before the onset of con-

TABLE II

Hemodynamic Findings in Seven Patients With Constrictive Pericarditis

Case (n)	HR (beats/min)	Pressures (mm Hg) RA (mean)	RV (S/D)	PA (S/D)	PWP (mean)	LV (S/D)	CO (liters/min)	Square Root Sign
1	68	24	55/28	50/28	26	100/28	4.0	Yes
2	76	14	32/12	32/14	14	140/14	2.6	Yes
3	80	18	38/20	36/20	16	142/21	5.2	Yes
4	78	17	36/20	34/20	22	140/24	6.0	Yes
5	76	17	28/18	24/18	18	125/20	3.0	Yes
6	84	18	40/18	40/20	20	140/20	5.3	Yes
7	82	21	39/21	39/22	22	115/22	3.8	Yes

CO = cardiac output; HR = heart rate; LV = left ventricular; PA = pulmonary arterial; PWP = pulmonary capillary wedge; RA = right atrial; RV = right ventricular; S/D = systolic/end-diastolic.

TABLE III

Left Ventricular Angiographic Findings in Seven Patients With Constrictive Pericarditis and in Seven Normal Control Subjects

	Constrictive Pericarditis (n = 7)	Normal Control Subjects (n = 7)
Wall motion		
Normal	6	7
Anterior hypokinesia	1	0
Akinesia	0	0
End-diastolic volume (cc)	102 ± 8	138 ± 12
Ejection fraction (%)	58 ± 3	63 ± 6

traction, and expressed as percent duration of diastole. Left ventricular filling curves were constructed for all patients included in this study.

Noninvasive and invasive studies: The purpose of this study would have best been served by simultaneous graphic recordings and left ventriculograms. However, the noise generated by the radiologic equipment made simultaneous recordings impossible. Fortunately, the heart rates of each patient were similar at the times when the phonocardiogram and left ventriculogram were obtained. To minimize further any error induced by this methodologic problem, all phonocardiographic and angiographic data were also expressed in percent of total duration of left ventricular diastole.

Patients: *Constrictive pericarditis:* Of the seven patients with constrictive pericarditis, four were men and three women. The mean age was 45 ± 7 years (mean ± standard deviation). The cause of the pericarditis, symptoms, signs and fluoroscopic findings in these seven patients are presented in Table I. Only five patients had an audible and recorded pericardial knock.

Cardiac catheterization data from these seven patients with constrictive pericarditis are displayed in Table II. All seven patients had sinus rhythm and a prominent *X* and *Y* descent in the right atrial pressure tracings; all had diastolic pressure equilibration in all intracardiac chambers and a "square root" sign in both the right and the left ventricular pressure tracing. Left ventricular angiography (Table III) revealed that six patients had totally normal left ventricular wall motion, and one patient had a hypokinetic anterior wall. End-diastolic left ventricular volumes in the seven patients averaged 102 ± 8 cc and the ejection fraction averaged 58 ± 3 percent.

All seven patients with constrictive pericarditis underwent pericardial stripping. Operative and pathologic notes were reviewed for the degree and location of pericardial fibrosis and for calcium deposition (Table IV).

Normal subjects: Seven patients underwent cardiac catheterization for evaluation of atypical chest pain. They served as a control group, having demonstrated normal findings on physical examination, electrocardiography, hemodynamic study, left ventriculography and coronary arteriography. End-diastolic volume in this control group averaged 138 ± 12 cc (Table III).

Statistical analysis: The two-tailed *t* test for unpaired samples was used to test the significance of observed changes. A probability (p) value of less than 0.05 was considered statistically significant.

Results

Left ventricular diastolic filling curves: In the seven normal subjects (Fig. 1) the composite diastolic filling curve had a rapid slope during the first 10 percent of diastole and a more gradual slope during the remaining 90 percent. At 30 percent of left ventricular diastole, 35 ± 4 percent of left ventricular filling had occurred.

Figure 2 compares the left ventricular diastolic filling curves of the five patients with constrictive pericarditis who had a pericardial knock with the composite filling curve of the normal patients. In constrictive pericarditis there was very rapid early diastolic filling, which reached a plateau at 30 to 40 percent of the duration of diastole. At that point, 85 ± 4 percent (63 to 98 percent) of diastolic filling was achieved as opposed to 35 percent in the control group. Figure 3 compares the diastolic filling curves of two additional patients with proved constrictive pericarditis who did not have a pericardial knock with the composite curve of the normal patients. These two patients had a slightly faster rate of early filling than that of normal subjects, but there was no plateau in the left ventricular filling curve. End-diastolic volume in the patients with constrictive pericarditis was significantly smaller than that in the normal control group (102 ± 8 versus 138 ± 12 cc, $p < 0.05$) (Table III).

TABLE IV

Phonocardiographic-Angiographic-Pathologic Correlations in Seven Patients With Constrictive Pericarditis

Case	HR (beats/min)	Pericardial Knock	Phonocardiographic Timing*		Angiogram: LV Volume Curve (sudden plateau)	Angiogram: Timing*		Operative Findings (fibrosis and/or calcium)
			ms	% Diastole		ms	% Diastole	
1	68	Yes	90	32	Yes	94	30	A-V sulcus + anterior wall
2	76	No	...	...	No	...	...	Anterior wall + lateral wall
3	80	Yes	95	40	Yes	112	40	Anterior + lateral + A-V sulcus
4	78	Yes	100	38	Yes	112	40	Lateral wall + A-V sulcus
5	76	Yes	120	30	Yes	128	30	A-V sulcus
6	84	No	...	...	No	...	...	Epicardium not adherent to pericardium
7	82	Yes	110	30	Yes	112	30	Anterior wall

* The differences in the phonocardiographic and angiographic timing of the pericardial knock were due to the use of 16 ms angiographic framing intervals.

A-V = atrioventricular; HR = heart rate; LV = left ventricle.

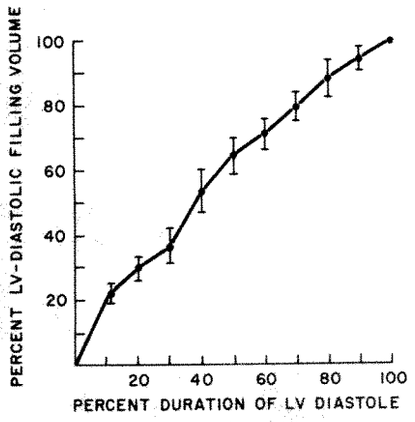


FIGURE 1. Left ventricular (LV) diastolic filling curve in seven normal control subjects, expressed as mean ± standard deviation of the mean.

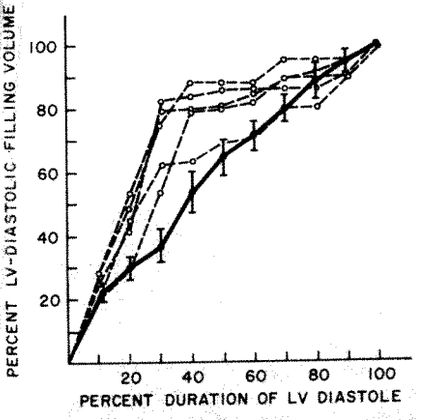


FIGURE 2. Left ventricular (LV) diastolic filling curves in five patients with constrictive pericarditis and a pericardial knock (**open circles and broken lines**) and left ventricular diastolic filling curve in seven normal control subjects, expressed as mean ± standard deviation (**solid circles and solid lines**).

Correlation of pericardial knock and left ventricular filling curve: Figure 4 presents the electrocardiogram, phonocardiogram, jugular venous pulse tracing and left ventricular filling curve in a typical patient with constrictive pericarditis and a knock. The beginning of left ventricular diastole corresponds to the second heart sound (aortic component) and the end of diastole to the first heart sound. The pericardial knock corresponds to the trough of the *Y* descent in the jugular venous tracing and to the beginning of the left ventricular filling curve plateau. Figure 5 presents the electrocardiogram, phonocardiogram, carotid pulse tracing and left ventricular filling curve in a patient with constrictive pericarditis who had no pericardial knock. No plateau in the left ventricular filling curve is evident.

Table IV correlates the phonocardiographic, angiographic and pathologic data in the seven patients with constrictive pericarditis. All patients had sinus rhythm at the time of the study, and their heart rates were similar during the graphic and angiographic studies. The five patients with a pericardial knock demonstrated a sudden plateau in the left ventricular filling curve. The timing of the pericardial knock in the phonocardiogram coincided with the initiation of the left ventricular filling curve plateau in all five patients. The two patients without a pericardial knock manifested no plateau in the left ventricular filling curve. However, they had typical hemodynamic and pathologic

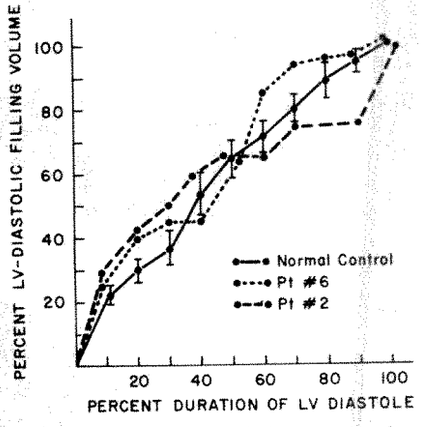


FIGURE 3. Left ventricular (LV) diastolic filling curves in two patients (Pt) with constrictive pericarditis and without a pericardial knock (Patients 2 and 6) (**solid circles and broken lines**) compared with the left ventricular diastolic filling curve in seven normal control subjects expressed as mean ± standard deviation (**solid circles and solid lines**).

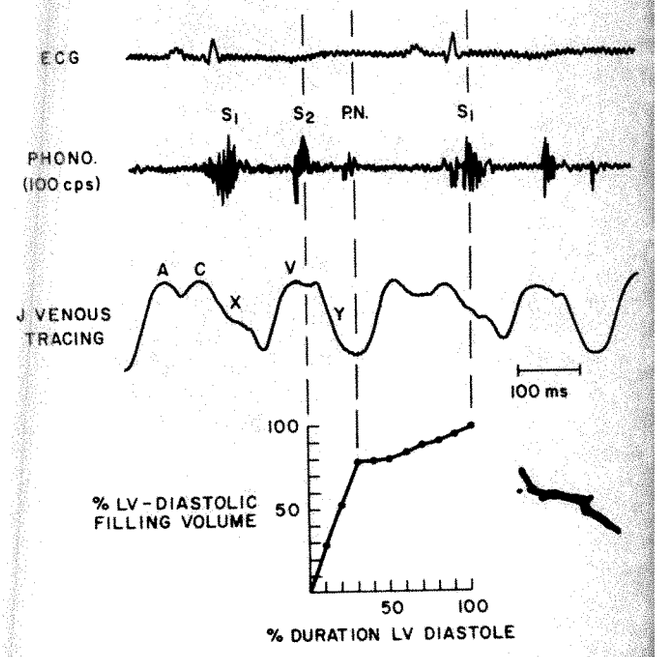


FIGURE 4. Electrocardiogram (ECG), phonocardiogram (PHONO.) with a 100 hertz filter, jugular (J) venous pulse tracing and left ventricular (LV) diastolic filling curve (expressed as percent of left ventricular diastolic filling volume and percent duration of left ventricular diastole) in Patient 1 with constrictive pericarditis and pericardial knock (P.N.). A = *A* wave; C = *C* wave; S_1 = first heart sound; S_2 = second heart sound; V = *V* wave; X = *X* descent; Y = *Y* descent. See text for explanation.

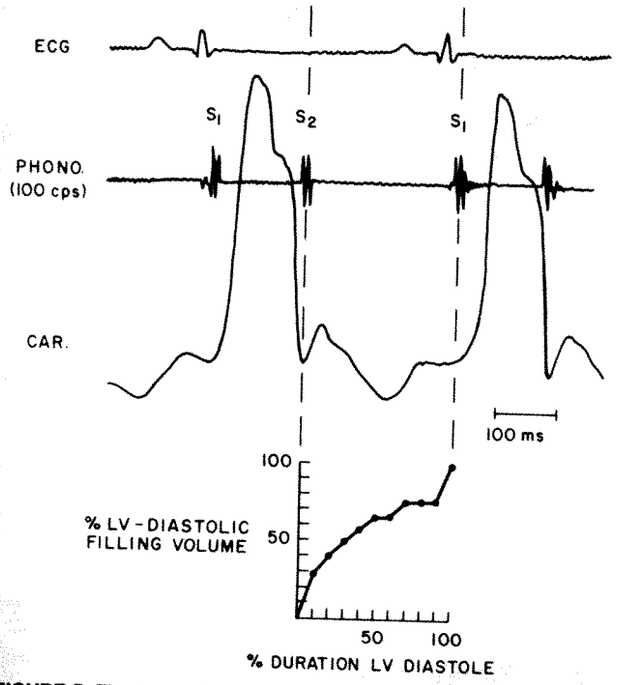


FIGURE 5. Electrocardiogram, phonocardiogram, carotid (CAR.) pulse tracing and left ventricular diastolic filling curve in Patient 2 with constrictive pericarditis but no pericardial knock. Abbreviations as Figure 4. See text for explanation.

findings of constrictive pericarditis, and their clinical condition improved after pericardiectomy.

Discussion

The seven normal control subjects demonstrated a typical pattern of left ventricular diastolic filling that is initially (first 10 percent of diastole) fast and then more gradual and uniform (Fig. 1). This angiographic finding is in agreement with previously reported studies.[16,17]

Pattern of sudden limitation of ventricular filling: The seven patients with constrictive pericarditis revealed two completely different patterns of left ventricular diastolic filling. Filling pattern A was characterized by a rapid filling period that lasted 30 to 40 percent of the total diastolic filling period, followed by a sudden and abrupt plateau. This plateau persisted until the end of diastole, except for a minimal increase in left ventricular filling near end-diastole, related to the atrial contribution to left ventricular end-diastolic volume (Fig. 2). Filling pattern B was characterized by slightly faster than normal filling in the early diastolic filling period (30 percent of diastole), but the curve had an overall shape similar to that of normal subjects (Fig. 3). Table IV discloses that all five patients with constrictive pericarditis and a pericardial knock demonstrated filling pattern A. Furthermore, the beginning of the left ventricular filling curve plateau corresponded temporally to the pericardial knock in each patient. The plateau in the left ventricular filling curve is a graphic representation of an abrupt pathologic cessation of diastolic filling. However, the two patients without a pericardial knock demonstrated filling pattern B. These patients, nevertheless, had the typical hemodynamics of pericardial constriction: elevated diastolic cardiac pressures and square root sign in the right and left ventricular pressure tracings. The angiograms were also characteristic of pericardial constriction: small left ventricular end-diastolic volume, normal left ventricular wall motion and normal left ventricular ejection fraction. They had operatively proved constrictive pericarditis (Table IV) and clinical improvement after pericardiectomy.

Causes for lack of abnormal filling pattern in two patients: Similar pattern B type findings have been reported by Mounsey[18] correlating phonocardiographic (pericardial knock) and hemodynamic measurements in the right side of the heart in patients with constrictive pericarditis. He described two patients who had no pericardial knock and a less abrupt and smoothly merging upstroke of the diastolic pressure dip in the right ventricular pressure recording. Pattern B could be explained by vascular volume depletion or by less severe constriction. Our two patients (Patient 2 and 6, Table II) had elevated right atrial, pulmonary wedge and ventricular diastolic filling pressures at the time of the cardiac catheterization, suggesting that they did not have significant volume depletion. One of these two patients (Patient 6, Table IV) had a thick fibrous pericardium, which was not adherent to the visceral pericardium (epicardium), suggesting that there was less severe constriction than in the pattern A patients, despite the typical hemodynamic findings. Another explanation for the lack of sudden limitation of left ventricular filling is that the right ventricle, which was not evaluated by angiography in this study, was less constricted than the left. The septum could then have provided continuing diastolic displacement at the expense of less impeded right ventricular filling. Alternatively, if the right ventricle was more constricted than the left, the left ventricle would have exhibited no sudden limitation of filling.

Mechanisms of the pericardial knock: The precise mechanism by which the sudden limitation of ventricular filling in constrictive pericarditis is converted to the sound of the pericardial knock is not clarified by our study, but two possibilities are suggested: (1) A "water-hammer" effect may be induced by abrupt deceleration of blood filling the ventricles, and the knock is produced by closely coupled secondary vibrations of chamber blood, ventricular walls, valves and pericardium, a mechanism similar to that proposed for the ventricular gallop sound. (2) A "sail-flop" phenomenon occurs, as in the cases of the opening snap of mitral stenosis or the ejection click of congenital aortic or pulmonary stenosis by which sudden tautening of a containing membrane (the pericardium in the current case) directly creates vibrations at audible frequencies which then are transferred to adjacent structures, such as the ventricular walls, chamber blood and chest wall tissues. Because both ventricles are usually involved by constriction, it is likely that they are involved in these phenomena, and that filling curves of the right ventricle would closely resemble those that have been demonstrated for the left ventricle in our study.

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Initiation and Termination of Ventricular Tachycardia by Supraventricular Stimuli

Incidence and Electrophysiologic Determinants as Observed During Programmed Stimulation of the Heart

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In 7 of 43 patients in whom a sustained ventricular tachycardia could be induced during programmed electrical stimulation by a single ventricular premature stimulus, an identical tachycardia could also be initiated by a single atrial premature stimulus. This phenomenon was observed only in those patients in whom the ventricular tachycardia could be induced by a single ventricular extrastimulus having a prematurity index (ratio between the longest ventricular premature stimulus interval resulting in tachycardia and the duration of the basic cycle length of the paced ventricular rhythm) above 54 percent. No single instance of initiation of ventricular tachycardia by atrial premature stimuli was observed in patients with a ventricular prematurity index below 54 percent or requiring more than one consecutive ventricular extrastimulus to have tachycardia initiated. Other features of patients showing initiation of ventricular tachycardia by atrial premature stimuli were a right bundle branch block configuration of the QRS complex during tachycardia in all seven patients and a relatively slow rate during tachycardia. In one patient ventricular tachycardia was terminated by a conducted atrial premature stimulus.

Instances of ventricular tachycardia initiated by a supraventricular stimulus have been reported in human beings.[1–8] However, no study has been reported of the incidence of this phenomenon or of its electrophysiologic determinants in a large series of patients with ventricular tachycardia. In this article these aspects are analyzed and their possible therapeutic implications discussed in a series of 54 patients with clinically documented recurrent episodes of sustained ventricular tachycardia in whom an identical arrhythmia was induced during a stimulation study.

Methods

Patients: Data on 54 patients having recurrent sustained ventricular tachycardia in whom the arrhythmia could reproducibly be initiated and terminated by programmed electrical stimulation of the heart were reviewed. In all patients the tachycardia initiated during the stimulation study was similar to the one clinically documented. In none of the patients was the tachycardia initiated during exercise or after a spontaneous atrial extrasystole. In all patients administration of drugs was discontinued at least five half-lives before the study.

Protocol: Methods of stimulation and recording used in our laboratory have previously been described.[6] All patients had an A-H interval during sinus rhythm (measured on the His bundle electrogram from the first fast deflection of the atrial electrogram to the beginning of the fast deflection of the His potential) of more than 60 ms and showed normal prolongation of the A-H interval after administration of atrial test stimuli and during atrial pacing at increasing rates. Anterograde conduction over an accessory atrioventricular (A-V) pathway was

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excluded by observing no change or an increase in the H-V interval after A-V conduction of atrial premature stimuli during atrial pacing at a regular paced rhythm and atrial pacing at increasing rates. The diagnosis of a ventricular origin of the tachycardia was based on the presence of a widened QRS complex (0.12 second or more) not preceded by a His bundle deflection or an H-V interval that was less than the interval recorded during sinus rhythm. After informed consent was obtained, single test stimulation during a regular paced rhythm as well as pacing at increasing rates was performed from the atrium and ventricle in all patients. Atrial and ventricular extrastimulus testing was performed at basic cycle lengths of 600 and 500 ms in all patients; if possible, a cycle length between 600 ms and the sinus cycle length was also utilized. If no tachycardia could be initiated using this protocol of stimulation, up to three ventricular premature stimuli were given during a ventricular paced rhythm at the same basic cycle lengths as previously stated. In all patients timed atrial and ventricular premature stimuli were given during tachycardia with use of the synchronizing circuit of the stimulator. All data were statistically analyzed using Student's t test.

Definition of terms: The following terms are used throughout the study:

V_1-V_2 during atrial extrastimulus testing: interval between the ventricular complex resulting from the last complex of the basic atrial rhythm and the ventricular complex that follows the atrial test stimulus.

V_1-V_2 during ventricular extrastimulus testing: premature stimulus interval of the ventricular extrastimulus delivered during a regular ventricular paced rhythm.

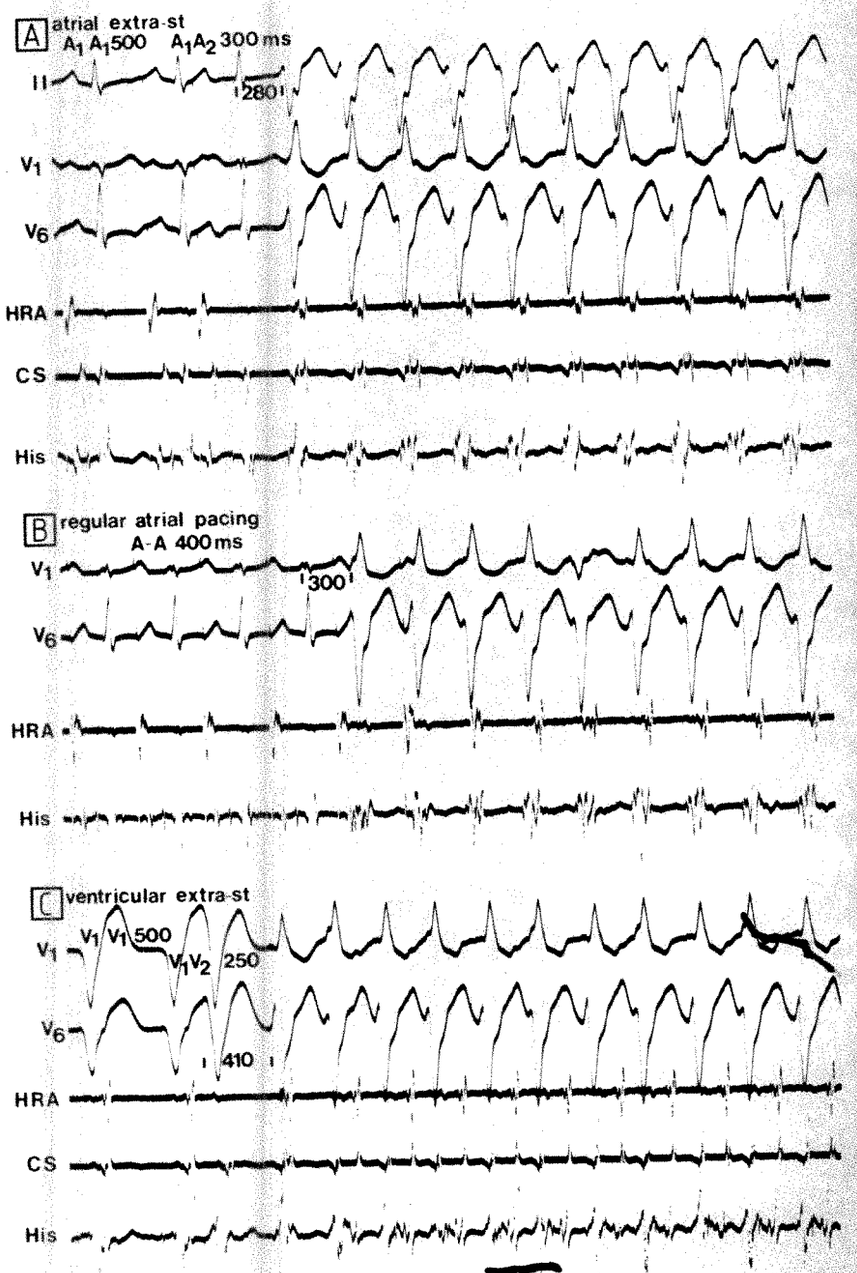


FIGURE 1. Initiation of ventricular tachycardia by **(A)** a critically timed right atrial premature stimulus (atrial extra-st) during atrial pacing, **(B)** rapid atrial pacing on reaching a pacing rate of 150 beats/min, and **(C)** a critically timed right ventricular premature beat (ventricular extra-st) during ventricular pacing. Simultaneous recordings of leads V_1, V_6, a high right atrial lead (HRA), a coronary sinus lead (CS) and a His bundle lead (His) are shown; in **A**, lead II is shown as well.

Prematurity index: ratio between the longest V_1-V_2 interval resulting in tachycardia during a ventricular paced rhythm and the basic cycle length (V_1-V_1) of the latter.

Results

Initiation of ventricular tachycardia: Ventricular tachycardia could reproducibly be initiated during programmed electrical stimulation of the heart in 54 patients. In all patients the induced tachycardia had the same configuration as that documented outside the cardiac laboratory. In 43 patients initiation of tachycardia could be accomplished by a single ventricular premature stimulus during ventricular pacing. In seven of these 43 patients a tachycardia with the same configuration and rate could also be initiated by a single atrial premature stimulus during atrial pacing. In all seven patients the QRS complex following the atrial premature stimulus was similar to the QRS complexes of the basic paced atrial rhythm. In two of the seven patients ventricular tachycardia could also be initiated by regular atrial pacing at increasing rates (Fig. 1). Because of the conduction characteristics of the A-V node, two patients had two zones of atrial premature stimulus intervals leading to ventricular tachycardia (Fig. 2 and 3). In none of the patients requiring two or more consecutive ventricular premature stimuli to initiate the ventricular tachycardia was the arrhythmia induced during atrial stimulation.

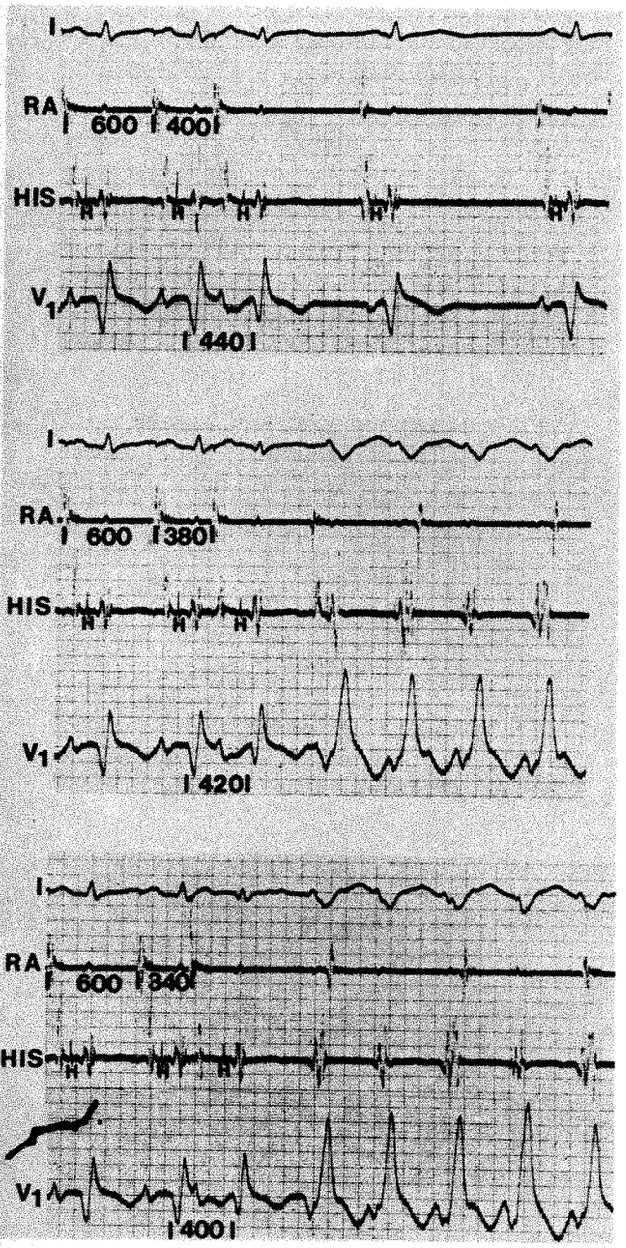


FIGURE 2. Upper panel, no initiation of ventricular tachycardia by an atrial premature stimulus of 400 ms during atrial pacing. **Middle panel,** ventricular tachycardia is initiated when an atrial premature stimulus given after an interval of 380 ms reaches the ventricle 420 ms after the ventricular complex resulting from the last stimulus of the basic atrial paced rhythm. **Lower panel,** further shortening of the atrial premature stimulus interval to 340 ms results in arrival of the impulse in the ventricle 400 ms after the last ventricular complex of the basic paced atrial rhythm and initiation of tachycardia.

Data from the seven patients in whom the tachycardia could be initiated by single atrial and ventricular premature stimuli (group A) were compared with those obtained in the 36 patients in whom ventricular tachycardia could be induced only by a single ventricular premature stimulus during ventricular pacing (group B). In three patients in group B, the longest V_1-V_2 interval leading to tachycardia during ventricular pacing was longer than the shortest V_1-V_2 interval attainable during atrial pacing at the same basic cycle length. In the remaining 33 patients of group B the shortest possible V_1-V_2 interval during atrial extrastimulus testing was longer than the longest V_1-V_2 interval required to initiate tachycardia during ventricular pacing.

In four patients in group A the longest V_1-V_2 interval leading to tachycardia during atrial extrastimulus testing was 20 to 40 ms shorter than the longest V_1-V_2 interval initiating tachycardia during a ventricular paced rhythm at the same basic cycle length. In the remaining three patients in group A the longest V_1-V_2 interval able to initiate tachycardia during atrial extrastimulus testing was similar (within a range of 10 ms) to the longest ventricular premature stimulus interval initiating tachycardia during ventricular pacing at the same basic cycle length.

Age, sex and cause of tachycardia: The age in group A ranged from 19 to 76 years (mean 45) and in group B from 19 to 81 years (mean 48). In group A 5 patients were male and 2 were female, whereas in group B 28 were male and 8 female. Four patients in group A and 25 in group B had an old myocardial infarction. Idiopathic ventricular tachycardia was present in 3 patients in group A and in 11 patients in group B. There were no statistical differences between groups A and B in age, sex or underlying heart disease.

QRS configuration during tachycardia, rate of tachycardia, tachycardia zone and prematurity index: All seven patients in group A had a right bundle branch block configuration during tachycardia and two had a complete right bundle branch block pattern

during sinus rhythm (Fig. 2 and 3). All patients in group A had a normal H-V interval during sinus rhythm. In 16 of the 36 patients in group B, the QRS complex during tachycardia had a left bundle branch block configuration (probability [p] <0.05).

Heart rates during ventricular tachycardia ranged from 120 to 180 beats/min (mean ± standard error of the mean 143 ± 20) in group A and from 110 to 220 beats/min (mean 172 ± 29) in group B. The widest zone of premature stimulus intervals resulting in tachycardia during ventricular extrastimulus testing with any of the basic cycle lengths that were used ranged from 80 to 300 ms (mean 134 ± 41) in group A and from 20 to 170 ms (mean 47 ± 21) in group B.

- *In assessing the ability to initiate ventricular tachycardia by ventricular premature stimuli,* we also determined the ratio between the longest V_1-V_2 interval leading to tachycardia during ventricular extrastimulus testing and the basic cycle length of the ventricular paced rhythm (V_1-V_1). This ratio was called the ventricular prematurity index and in patients in group A it ranged from 55 to 85 (mean 71 ± 11) percent and in group B from 32 to 52 (mean 41 ± 8) percent. These differences between groups A and B in QRS configuration and rate during tachycardia, the zone of premature stimulus intervals resulting in tachycardia and ventricular prematurity index of the longest V_1-V_2 interval leading to tachycardia during ventricular extrastimulus testing were statistically significant (p <0.01).

Termination of ventricular tachycardia by an atrial premature stimulus: In 10 patients atrial premature stimuli given during tachycardia were conducted to the ventricles. This resulted in fusion complexes in four patients and complete "captures" in six. In only one patient (in group B) could the tachycardia be terminated by a conducted supraventricular impulse. As shown in Figure 4, the tachycardia that had a rate of only 110 beats/min could be terminated by both a single ventricular premature stimulus and a conducted single atrial extrastimulus. The maximal rate of this tachycardia observed during the stimulation study was 120 beats/min (Fig. 5).

Discussion

Isolated examples of ventricular tachycardia induced after supraventricular impulses have previously been reported.[1–4,7,8] In the largest series of ventricular tachycardia induced by programmed electrical stimulation of the heart so far reported,[5,6,9] the characteristics and implications of the initiation of this arrhythmia by supraventricular stimuli were not analyzed.[5,6,9]

Incidence: Initiation of ventricular tachycardia by supraventricular impulses is not rare. In this series of 43 patients in whom a ventricular tachycardia could reproducibly be initiated during programmed electrical stimulation of the heart by a single timed ventricular premature impulse, an identical tachycardia could also be induced by atrial premature stimuli in 7 patients. This represents an incidence rate of 16 percent. In contrast, termination of a ventricular tachycardia by supraventricular extrastimuli is a very rare observation and was found in only one patient in our series.

Electrophysiologic Determinants

Initiation of ventricular tachycardia by supraventricular stimuli: This phenomenon seemed to be determined in our patients by the ease of initiation of

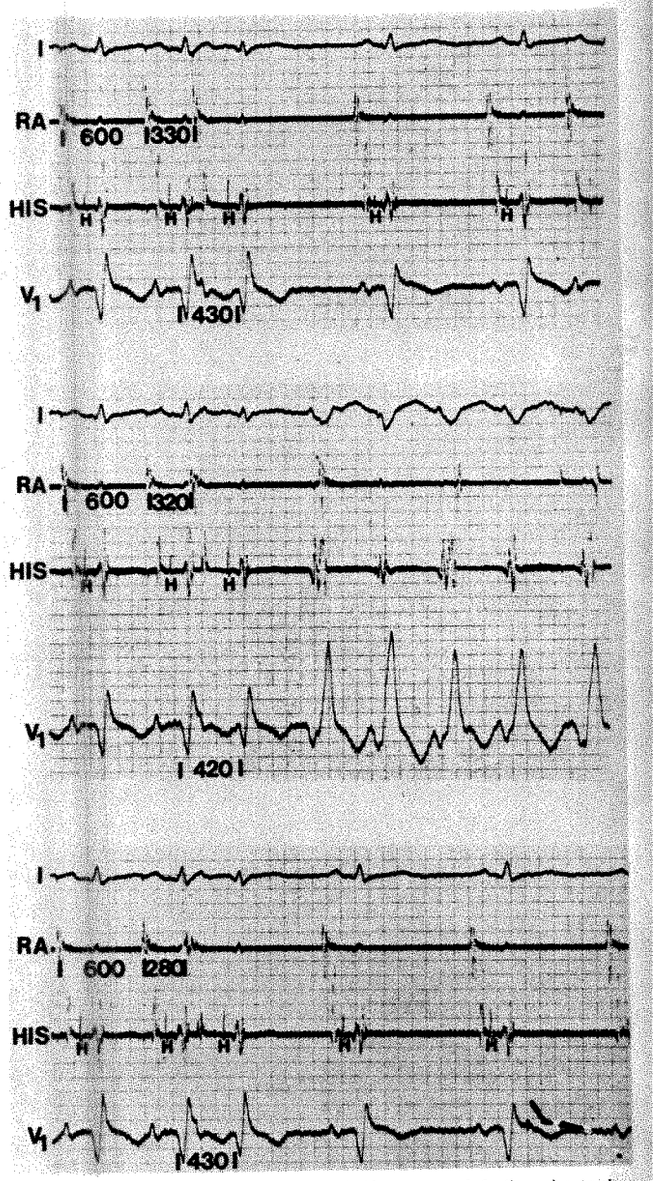


FIGURE 3. Same patient as in Figure 2. **Upper panel,** further shortening of the atrial premature stimulus interval to 330 ms results in prolongation of atrioventricular (A-V) nodal conduction time leading to delayed arrival of the impulse in the ventricle. Now the interval between this ventricular complex and the preceding ventricular complex measures 430 ms, which exceeds the upper limit of the tachycardia zone (420 ms, **middle panel** Fig. 2) and no tachycardia is initiated. **Middle panel,** when the atrial premature stimulus is given 10 ms earlier, the interval at the ventricular level lengthens again to 420 ms with initiation of tachycardia. **Lower panel,** further shortening of the atrial premature stimulus interval results in arrival at the ventricular level outside the upper limit of the tachycardia zone.

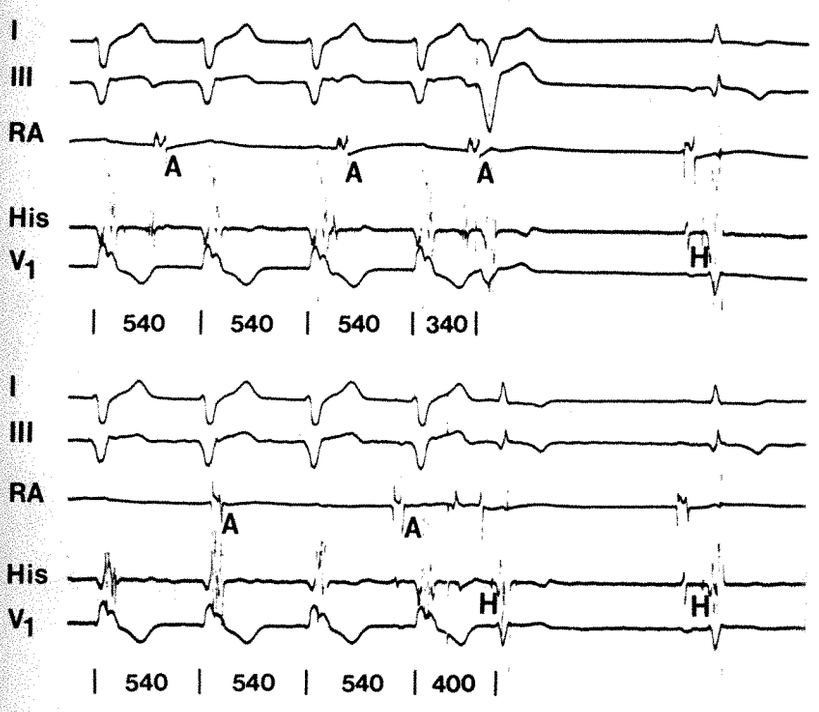


FIGURE 4. Termination of a ventricular tachycardia with a slow rate (110 beats/min) by an electrically induced ventricular (**upper panel**) and atrial (**lower panel**) premature stimulus. **Upper panel,** 3: 2 ventriculoatrial (V-A) Wenckebach conduction is present. **Lower panel,** termination of tachycardia by the conducted atrial premature impulse is possible because of the low rate during tachycardia, permitting arrival of the atrial impulse in the ventricle (in spite of delay in the atrioventricular (A-V) node) early enough to enter the ventricular reentry circuit to terminate tachycardia. The slow rate of the tachycardia might suggest this arrhythmia to be an example of an accelerated idioventricular rhythm. However, the arrhythmia could reproducibly be initiated by premature ventricular stimuli during ventricular pacing. We have never observed this phenomenon during stimulation studies in patients with documented accelerated idioventricular rhythm.

the tachycardia. First, initiation of ventricular tachycardia by atrial premature stimuli was observed only in patients in whom no more than a single ventricular premature stimulus was required to induce the arrhythmia. Second, in the latter group of 43 patients, atrial premature stimuli were able to initiate ventricular tachycardia only in those patients in whom the prematurity index of the longest V_1-V_2 interval resulting in tachycardia during ventricular extrastimulus testing was above 54 percent.

No overlap in prematurity index existed between group A (patients in whom ventricular tachycardia was inducible by both one ventricular and one atrial premature stimulus) and group B (tachycardia induced by only one ventricular extrastimulus during ventricular pacing). Thus, when a ventricular tachycardia can be induced by a ventricular extrastimulus with a prematurity index above 54 percent, it seems likely that the same tachycardia will be initiated by atrial premature impulses.

The time of arrival of the initiating impulse to the ventricles is not the only factor determining the induction of a ventricular tachycardia by a supraventricular stimulus. This is illustrated in three of our patients in whom tachycardia could be initiated only by a ventricular premature stimulus even though the tachycardia zone during ventricular extrastimulus testing occurred at longer V_1-V_2 intervals than the shortest V_1-V_2 interval attainable during atrial extrastimulus testing at the same basic cycle length. In addition, four patients in group A the longest V_1-V_2 interval resulting in the initiation of ventricular tachycardia during atrial extrastimulus testing was shorter than the longest V_1-V_2 interval required to induce tachycardia during ventricular stimulation at the same basic driving rate. These observations suggest that the site of stimulation and the direction and spread of the excitatory wave also play important roles in the initiation of ventricular tachycardia.[6,10]

Although it is understandable that patients with ventricular tachycardia whose arrhythmia can be initiated by a supraventricular stimulus have a wide tachycardia zone and a longer prematurity index during testing by the ventricular extrastimulus technique, the lower mean ventricular rate during tachycardia in patients in group A than in those in group B is more difficult to explain. As demonstrated by Josephson et al,[11] the reentry circuit underlying most instances of chronic recurrent sustained ventricular tachycardia is very likely of small size, suggesting that slow conduction is the main electrophysiologic determinant of the heart rate during ventricular tachycardia. If in a region of impaired conduction a certain value of refractoriness exists, the slower the conduction velocity within a reentry circuit, the easier it will be to reexcite the initially blocked region and to initiate tachycardia. This is probably why a statistically significant relation was found between the ease of initiation of tachycardia (as defined by the prematurity index) and the ventricular rate during the arrhythmia in those patients in whom a single conducted atrial premature stimulus was the only requirement to create unidirectional block (refractoriness) within the circuit.

Termination of ventricular tachycardia by supraventricular stimuli: The rarity of this phenomenon (observed in only 1 of 43 patients) is not surprising. If reentry is the mechanism of the arrhythmia, termination of the tachycardia by a premature stimulus re-

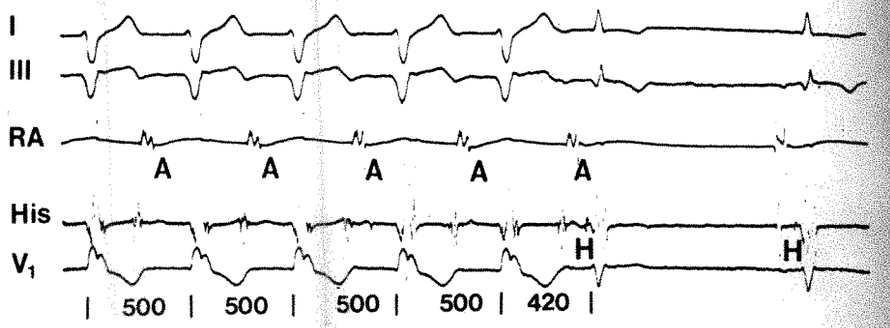


FIGURE 5. Same patient as in Figure 4. During ventricular tachycardia 1:1 ventriculoatrial (V-A) conduction is present. The increase in V-A conduction time after the fifth QRS complex of the tachycardia is followed by an atrioventricular (A-V) nodal echo impulse. This echo impulse terminates tachycardia spontaneously.

quires invasion into the reentry circuit and creation of refractoriness ahead of the circulating impulse by the premature stimulus. Only when the rate of the ventricular tachycardia is relatively slow can a premature supraventricular impulse pass the delaying area of the A-V node and capture the ventricles with sufficient prematurity as to enter the reentry circuit at the appropriate time to terminate the arrhythmia. Rates of 110 to 120 beats/min are not frequent during ventricular tachycardia,[5,9] although in a previous report from our group[12] rates below 130 beats/min were found in 9 of 70 different ventricular tachycardias observed in 62 patients.

In the patients in this study the rather slow ventricular tachycardia was observed to terminate not only after a conducted atrial premature stimulus but also spontaneously by an A-V nodal echo impulse (Fig. 4 and 5). This type of termination of ventricular tachycardia by a supraventricular impulse should be differentiated from the also rare observation of termination by a nonconducted supraventricular impulse of a tachycardia based on a reentrant mechanism using the bundle branch system.[13]

QRS configuration in ventricular tachycardia induced by atrial impulses: The association between the ability to induce a ventricular tachycardia by supraventricular impulses and a right bundle branch block configuration during tachycardia has been found in other reported examples.[1,4,6,8] We cannot offer an explanation for our finding that all the ventricular tachycardias that were induced by both single atrial and ventricular premature impulses had a right bundle branch block configuration.

Comparison with previously reported electrophysiologic findings: The observations mentioned previously are in accord with the electrophysiologic characteristics of the patient reported on by Denes et al.[5] in whom a ventricular tachycardia could be induced by an atrial extrastimulus. Ventricular tachycardia in their patient had a right bundle branch block configuration and a rate between 130 and 180 beats/min. In addition, this tachycardia could be induced by a single ventricular extrastimulus within a wide zone of premature impulse intervals (180 ms), the ventricular prematurity index being 67 percent. In another patient in their series, ventricular tachycardia could be induced after cessation of atrial pacing as well as by a single ventricular premature stimulus. Data to assess whether this patient did or did not have the other characteristics found in our patients are not given in the study.

Josephson et al.[9] described a patient in whom ventricular tachycardia was induced by rapid atrial pacing and by single ventricular extrastimuli. No additional information was given to allow comparison with our patients. Finally, Zipes et al.[8] described three patients in whom a ventricular tachycardia was initiated by supraventricular impulses. In the only patient in whom the ventricular tachycardia could be initiated by single atrial premature stimuli, the arrhythmia was not induced by ventricular premature stimuli. The number of basic cycle lengths used during ventricular extrastimulus testing and data on whether this technique was applied at one or more ventricular endocardial sites are not given. As discussed elsewhere,[6] both features (basic cycle length and site of stimulation) are important determinants of the ease of initiation of ventricular tachycardia. These factors might account for the apparent discrepancies between the patient of Zipes et al. and our patients.

Clinical Implications

The observation that ventricular tachycardia can be initiated by an atrial premature stimulus is of clinical importance. In fact, clinical examples of initiation of both ventricular tachycardia and ventricular fibrillation after supraventricular conducted impulses have been reported.[1,7,14] One of the main practical implications of our study may be related to the possible modifications in the ease of initiation of ventricular tachycardia after administration of antiarrhythmic drugs. These might occur when the drug does not significantly affect the A-V nodal properties but induces in the ventricular reentry circuit a reduction in conduction velocity that is greater than the prolongation of refractoriness. We[15] previously reported on the effect of procainamide in 12 patients with recurrent sustained ventricular tachycardia. After the administration of procainamide in all eight patients in whom the arrhythmia was still inducible, ventricular premature stimuli given at longer premature stimulus intervals were able to initiate ventricular tachycardia. In three of these eight patients the prematurity index increased from a value below 48 percent to one above 56 percent after administration of antiarrhythmic drugs. The observation of initiation of

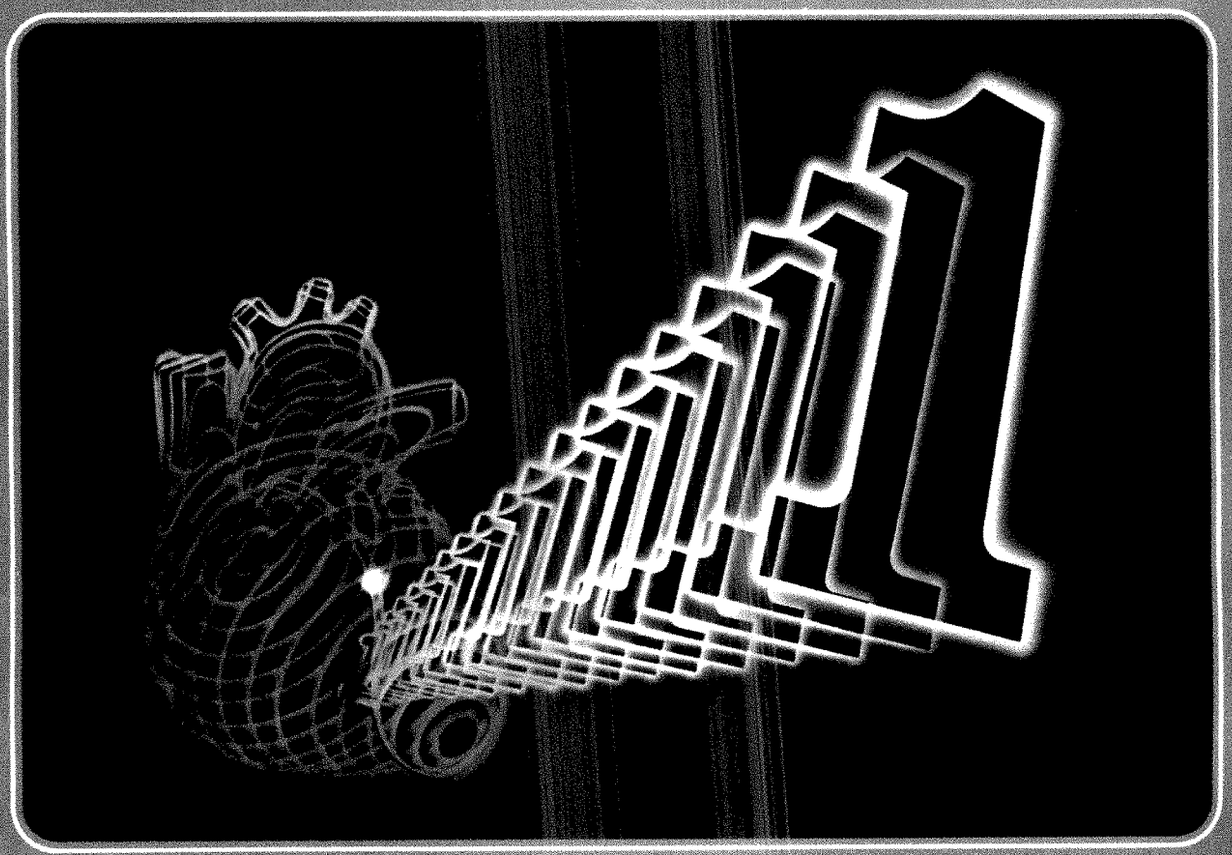
ventricular tachycardia by later ventricular premature stimuli after the administration of procainamide was also made by Horowitz et al.[16] This finding suggets that, under these circumstances, an atrial premature stimulus might have been able to induce ventricular tachycardia. Unfortunately, we did not test in our patients the effect of atrial premature stimuli on the initiation of tachycardia after the administration of procainamide. However, our findings suggest that in some patients ventricular tachycardia may not be prevented by giving a drug that can abolish ventricular premature complexes unless it also simultaneously eliminates atrial extrasystoles or significantly prolongs conduction time and refractoriness in the A-V node, or both.

Our study indicates that formation of an abnormal impulse at the supraventricular level may play a more important role in the initiation of ventricular tachycardia than previously realized. Although all our patients had normal A-V nodal function, such a mechanism would theoretically be further facilitated by abbreviation of the refractory period and acceleration of the conduction velocity of the A-V node by sympathomimetic or parasympatholytic influences. In all our patients the conducted supraventricular stimulus had a ventricular activation pattern that was similar to the one seen after the basic paced atrial rhythm. In view of the role of spread of ventricular excitation in the initiation of a ventricular reentrant mechanism,[6,10] it can be suspected that in some patients initiation of ventricular tachycardia by a conducted supraventricular impulse will only occur if the premature impulse is aberrantly conducted through the ventricle.

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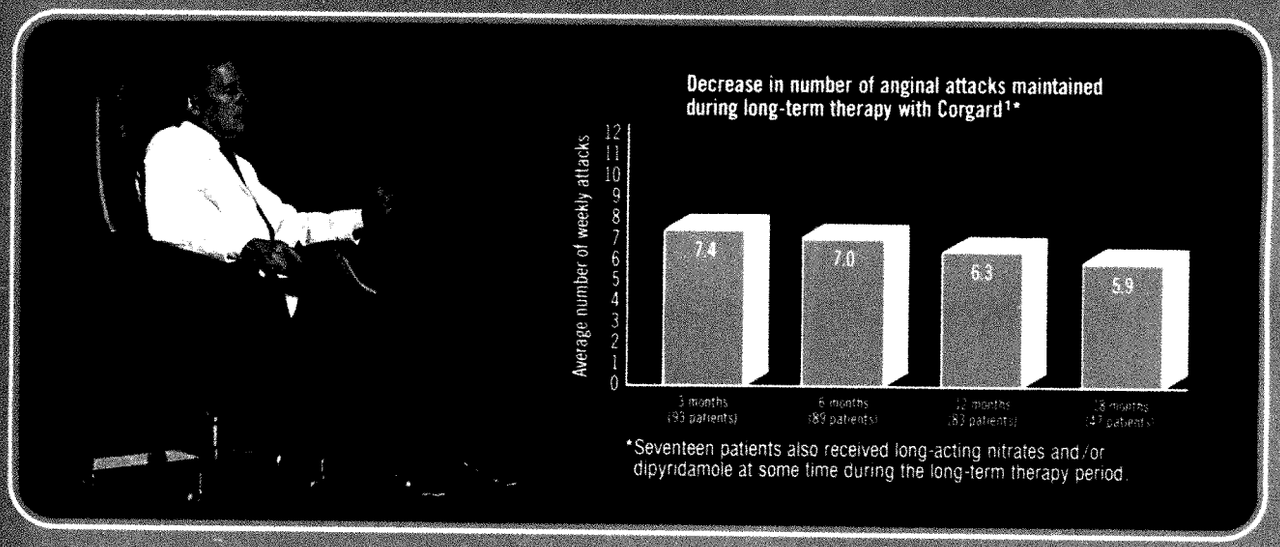


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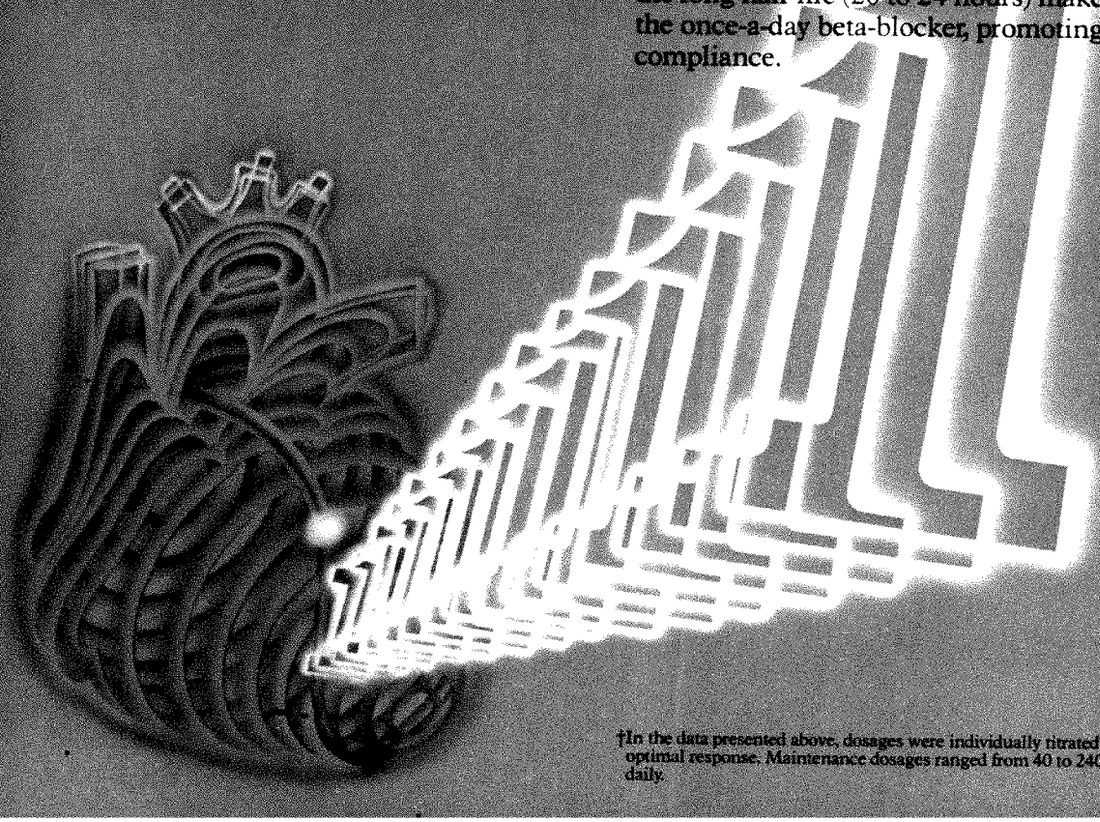
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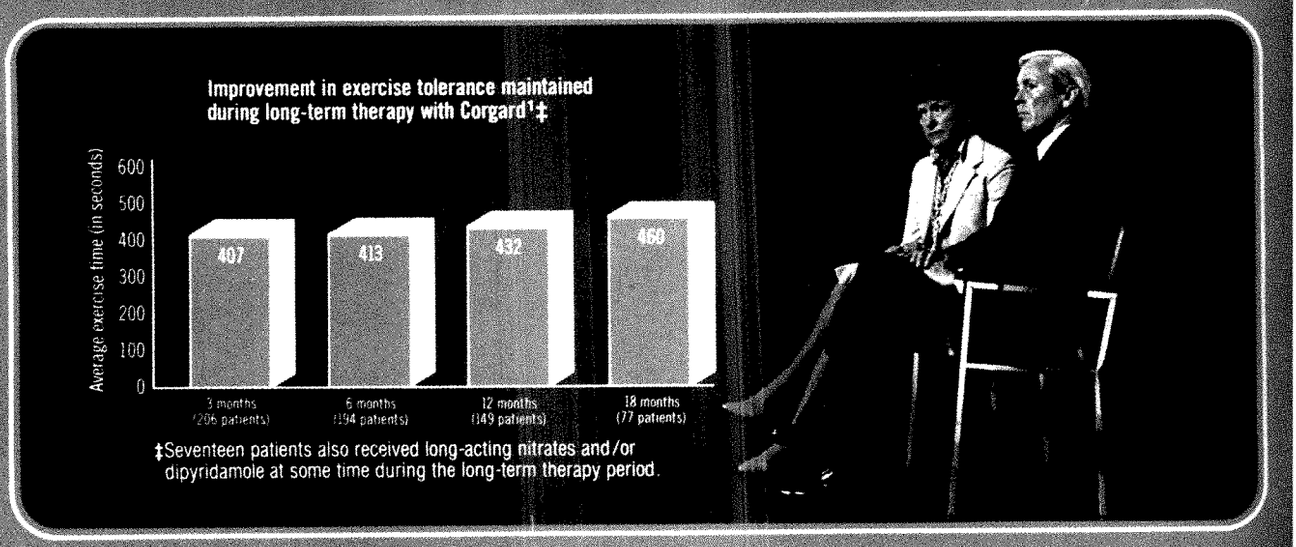
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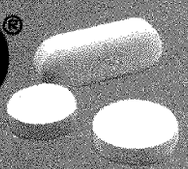
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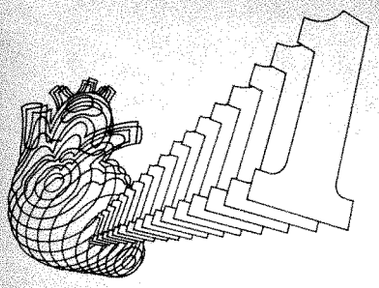
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Effective control of angina pectoris... and hypertension



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Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

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Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

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Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. • **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 16(mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, or 120 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:

1. Data on file, Squibb Institute for Medical Research.

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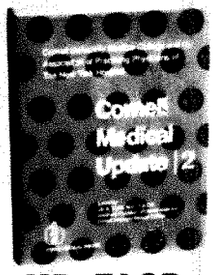
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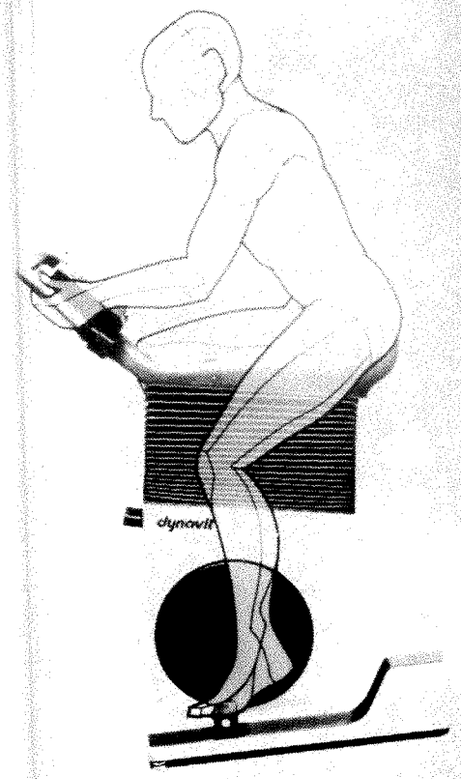
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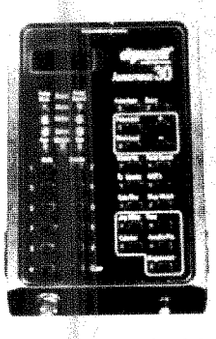
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A dynamometer which measures physical work rates

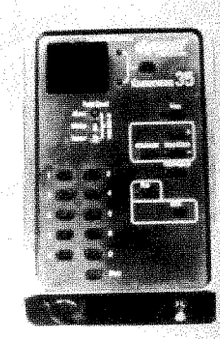


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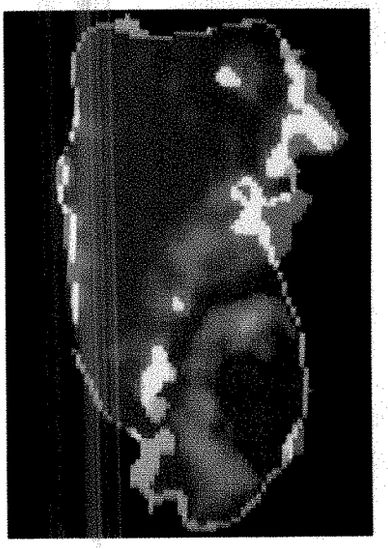
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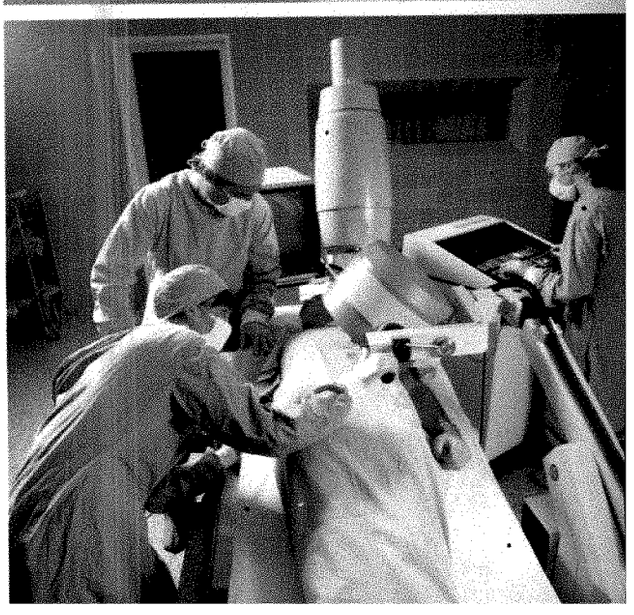


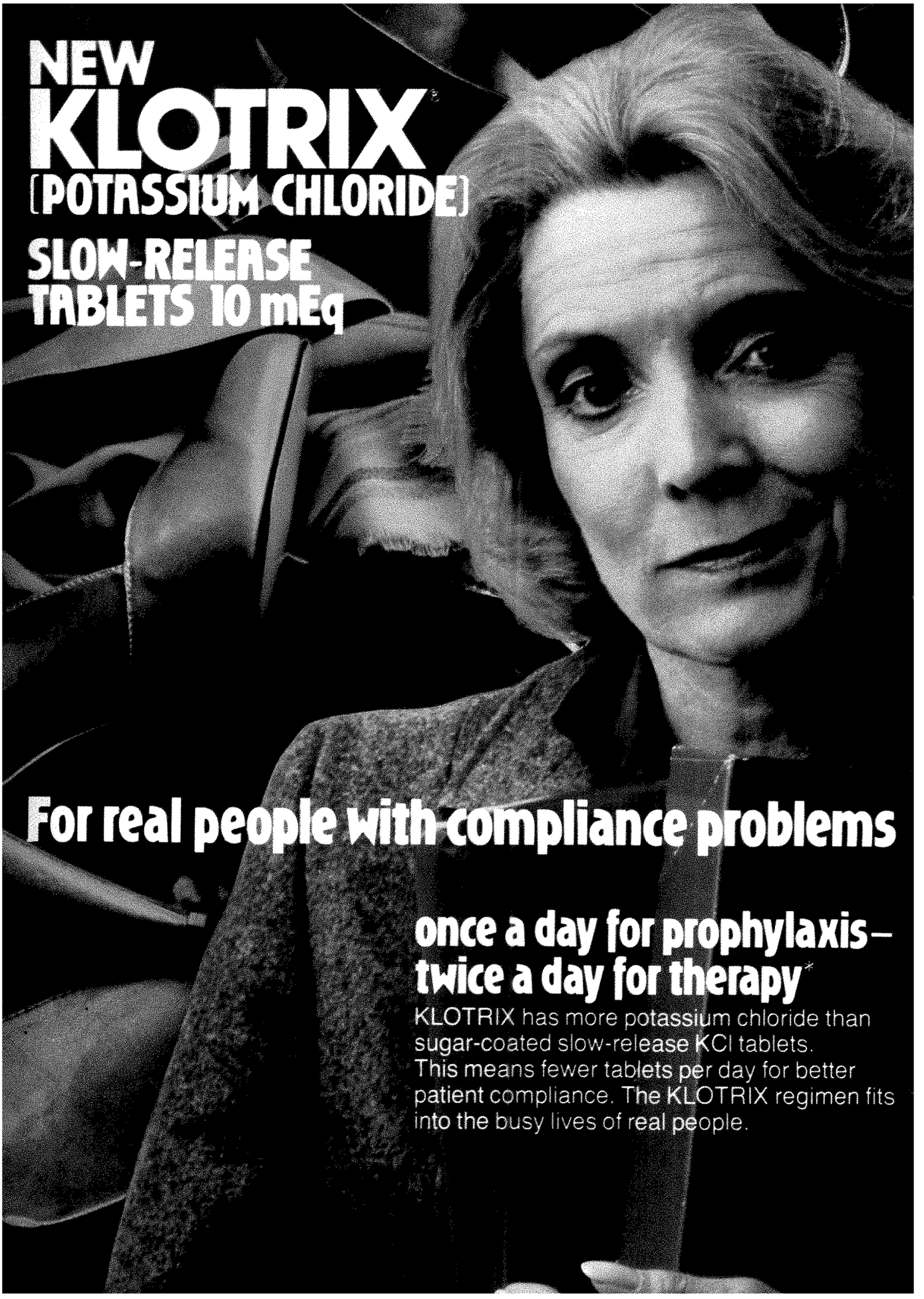
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PHARMACEUTICAL DIVISION
*Please see following page for summary of prescribing information.
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NEW KLOTRIX®
(POTASSIUM CHLORIDE)
SLOW-RELEASE TABLETS 10 mEq

DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS—BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE Usual dietary intake potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: KLOTRIX slow-release tablets must be swallowed whole and never crushed or chewed.

HOW SUPPLIED Bottles of 100.

Mead Johnson PHARMACEUTICAL DIVISION

NITROSTAT®
(nitroglycerin tablets, USP)

INDICATIONS
Nitrostat is indicated for the prophylaxis, treatment and management of patients with angina pectoris.

CONTRAINDICATIONS
Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

HOW SUPPLIED
Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

0.15 mg (1/400 grain): N 0071-0568-24 [06]—bottle of 100 tablets;
N 0071-0568-13—Convenience Package.

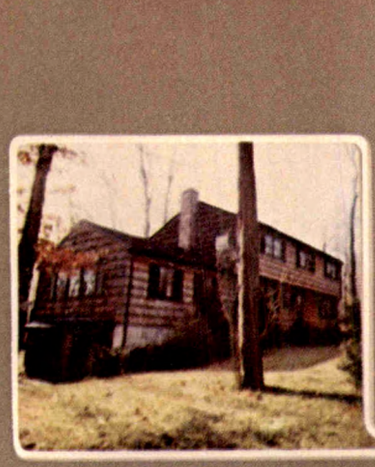
0.3 mg (1/200 grain): N 0071-0569-24 [06]—bottle of 100 tablets;
N 0071-0569-13—Convenience Package.

0.4 mg (1/150 grain): N 0071-0570-24 [06]—bottle of 100 tablets;
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0.6 mg (1/100 grain): N 0071-0571-24 [06]—bottle of 100 tablets;
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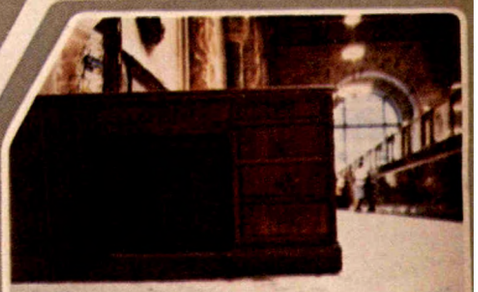
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Your angina patients will feel better protected.

Nitrostat®

(nitroglycerin tablets, USP) 4×25s

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For brief summary of the prescribing information, please see

*Five-year expiration date when stored at recommended storage conditions in an unopened bottle. Data on file.

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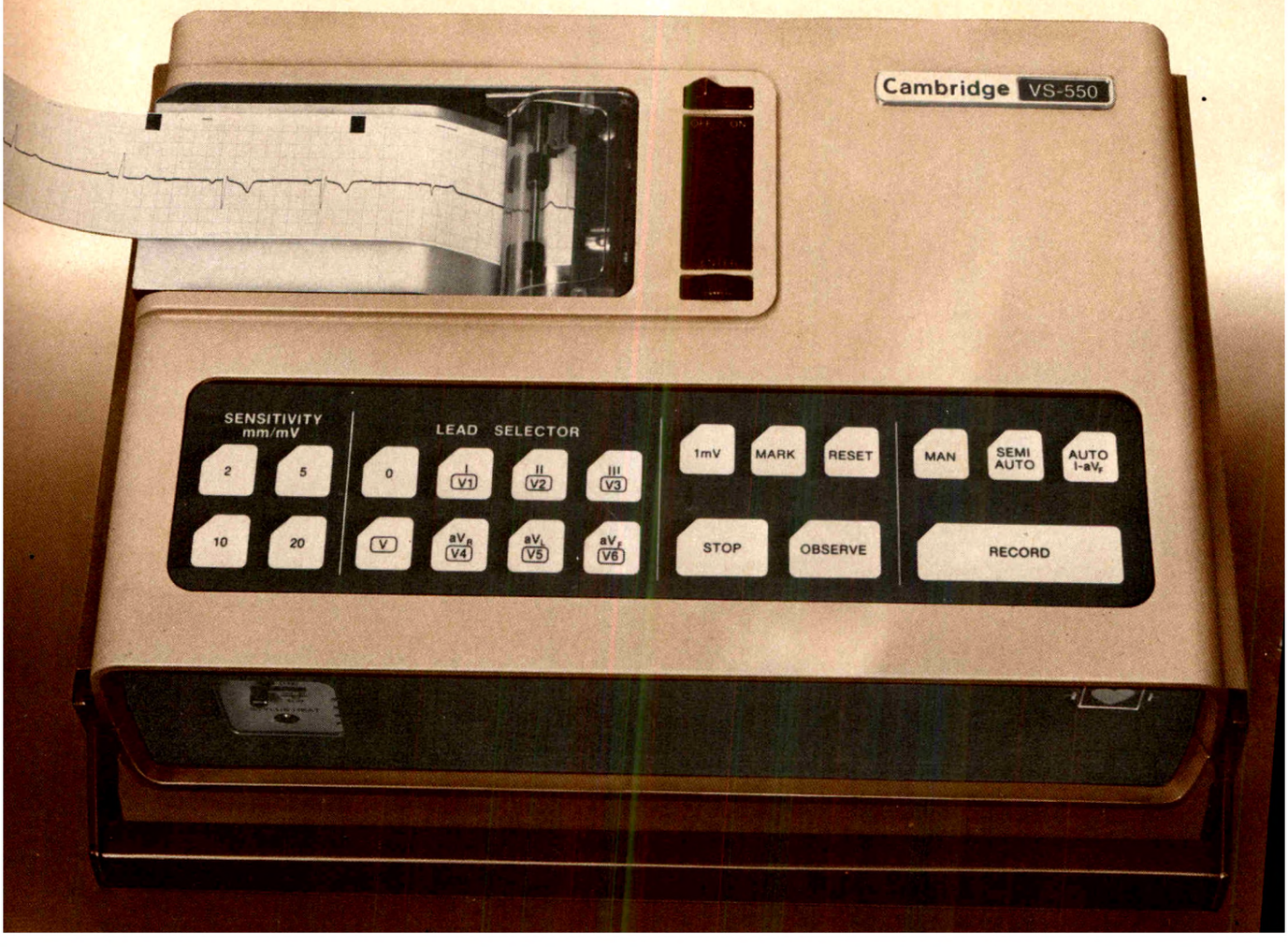
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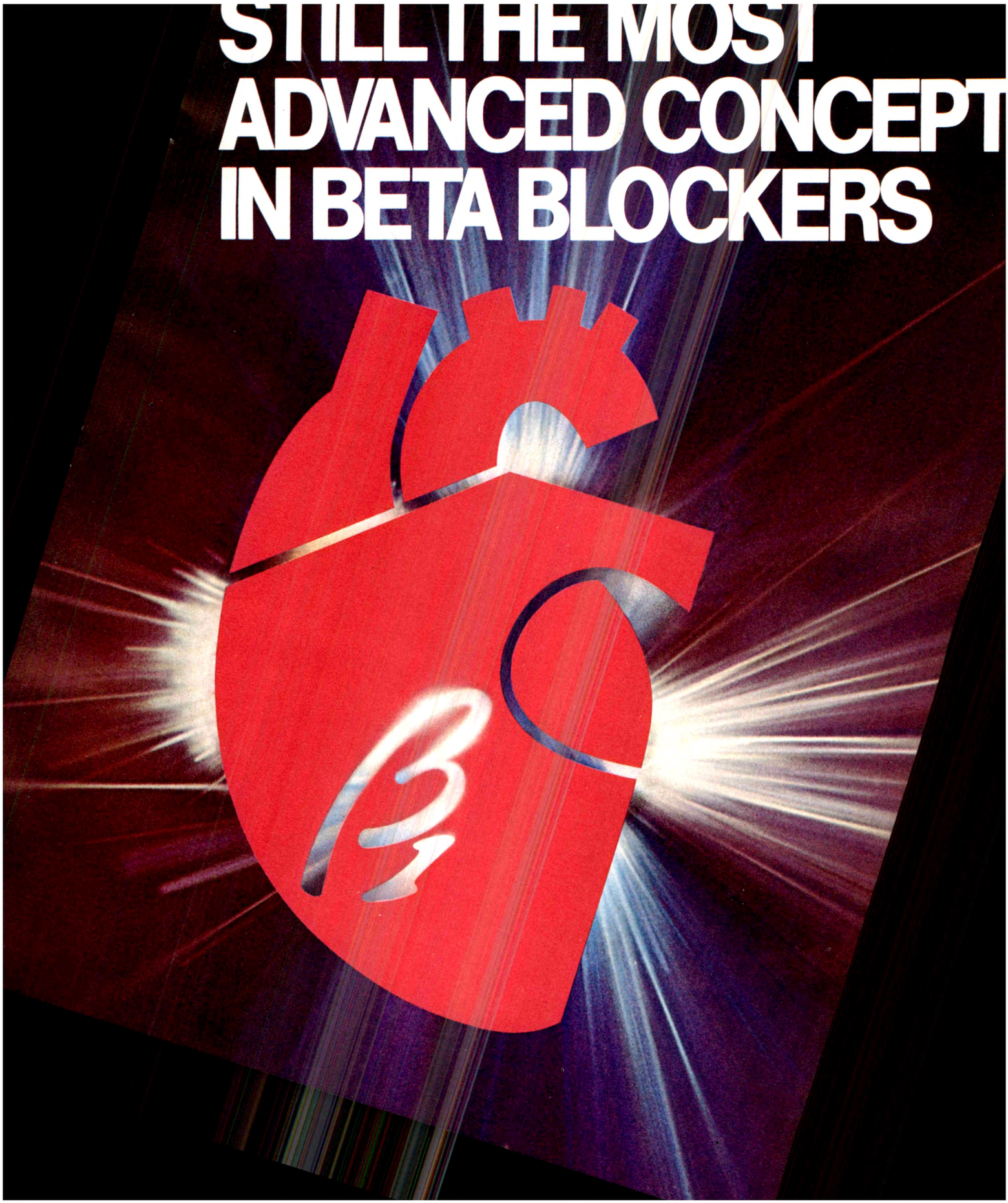
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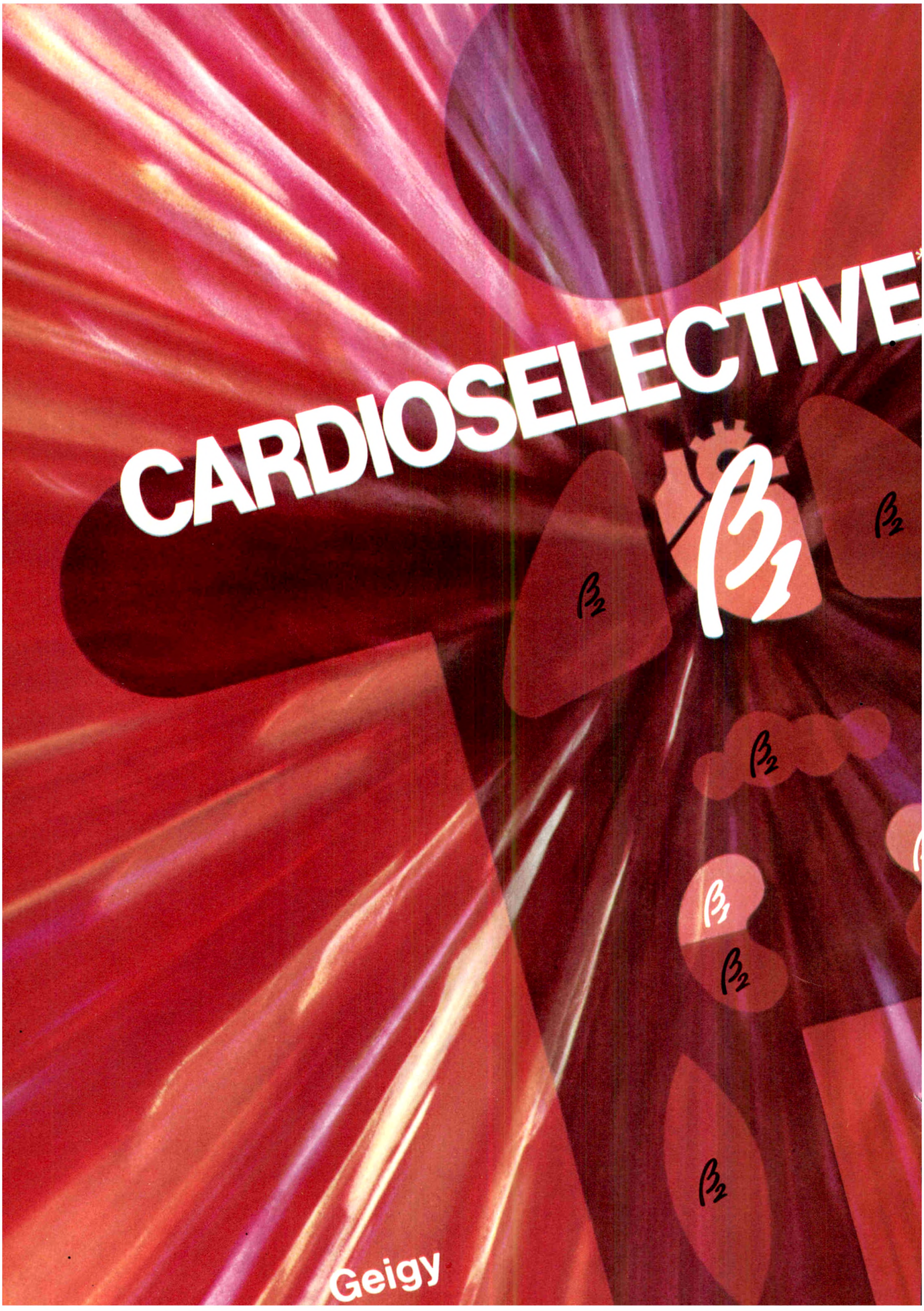
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exerts a relative preference for beta-one receptors.

WORKS WHERE IT SHOULD– NOT WHERE IT SHOULDN'T– IN HYPERTENSION

By concentrating its action on the beta-one receptors involved in blood pressure control and to a large extent—at usual therapeutic dosages—avoiding the unwanted effects of beta-two blockade, Lopressor offers potential benefits not available with the nonselective beta blockers.

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Propranolol, due to beta-two blockade, causes a greater reduction in muscle blood flow than does Lopressor.

REDUCES THE PRESSOR EFFECT OF EPINEPHRINE[2]
Propranolol augments the pressor effect of epinephrine, while Lopressor reduces the pressor effect.

BETTER TOLERABILITY IN PATIENTS WITH ASTHMA[3]
At an antihypertensive dosage (100 mg daily) there was no difference in FEV, and no patients reported any influence on their asthma.

Lopressor should be used with caution in patients with bronchospastic disease. Since beta-one selectivity is not absolute, bronchospastic patients should receive a beta-two-stimulating agent concomitantly. For complete details, see the Warnings section of the prescribing information.

Please see next page for brief summary of prescribing information.

Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 100 or less.

Allergic: Pruritus has occurred in less than 1 of 1(patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety c adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effec of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

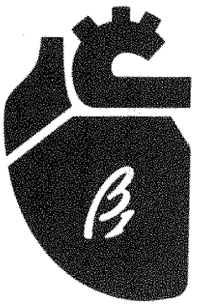
Dispense in tight, light-resistant container (USP)

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For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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Kinetics of Antifibrillatory Effects of Bretylium: Correlation With Myocardial Drug Concentrations

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To determine the kinetics of the antifibrillatory effects of bretylium tosylate and to assess the relative importance of myocardial versus serum drug concentrations, studies were performed in 32 dogs after they received bolus injections of bretylium tosylate (6 mg/kg or 2 mg/kg body weight) or saline solution. Parallel determinations were made of drug concentrations in serum and myocardium, together with antifibrillatory and electrophysiologic effects, both with and without 2 minutes of coronary ischemia produced by temporary coronary ligation. Serum bretylium concentration decreased rapidly after intravenous injection, whereas myocardial concentrations increased gradually, peaking at 1.5 to 6 hours in both open and closed chest dogs. The ratio of myocardial to serum drug concentration increased to 6.4 to 12.6 at 12 hours. Parallel elimination of the drug in serum and myocardium occurred thereafter, with elimination half-life of 10.5 hours (closed chest dogs).

Electrophysiologic and antifibrillatory effects paralleled myocardial rather than serum drug kinetics with peak effects at 3 to 6 hours. The ventricular effective refractory period was 24 to 26 ms greater at 3 hours in dogs treated with the drug than in those receiving saline solution. The ventricular fibrillation threshold increased 6 to 10-fold after 2 mg/kg of the drug was given at 3 to 6 hours in dogs both with and without ischemia in comparison with that in control animals treated with saline solution. The average increase in threshold exceeded 12-fold after administration of 6 mg/kg of the drug (2 minutes to 12 hours). The repetitive ventricular response threshold 3 hours after drug administration increased 5-fold after 2 mg/kg and 18-fold after 6 mg/kg of the drug was administered in dogs with or without ischemia.

These studies elucidate canine serum and myocardial drug kinetics of bretylium, quantify the prolonged antifibrillatory effect of this drug with its delayed maximal effect and emphasize the importance of tissue levels of bretylium in determining drug action.

Rational therapy with antiarrhythmic drugs is predicated on an understanding of pharmacokinetics and mechanisms of action.[1,2] Therapeutic effects depend on drug concentrations at sites of action. In the absence of techniques to determine concentrations at myocardial sites, drug concentrations in blood have been used to estimate expected drug response or adverse effects. However, these correlations may not be valid in drugs heavily concentrated in myocardial tissue, particularly during short-term administration when conditions of equilibrium do not apply.[2]

Bretylium tosylate is an antiarrhythmic drug recently approved for general use in therapy of refractory ventricular tachyarrhythmia.[3,4] Initially introduced more than 20 years ago as an antihypertensive drug, it proved ineffective because of rapid development of tolerance and erratic absorption with oral dosing. Bacaner[5] first discovered its antifibrillatory potential more than 10 years ago, and championed its application as an antiarrhythmic agent.

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During short-term administration, bretylium displays a biphasic effect on the cardiovascular system.[6,7] An initial increase in blood pressure accompanied by tachycardia is a manifestation of local catecholamine release at adrenergic nerve endings.[6,8] This is followed by a decrease in blood pressure and relative bradycardia, a manifestation of the drug's antiadrenergic effect. The latter is usually the predominant effect. The electrophysiologic effects of bretylium are complex and their relation to antiarrhythmic effects is as yet unclear.[9,10] The direct antiadrenergic as well as early sympathomimetic effects during administration have all been mentioned as potential contributing mechanisms. An increase in the ventricular fibrillation threshold was described more than a decade ago in dogs treated with bretyllium on a short-term basis,[5] but more recently questions concerning the drugs antifibrillatory as well as its antiarrhythmic effects have again been raised.[4]

The chemical and pharmacologic effects of bretylium place it in a class separate from other currently available antiarrhythmic drugs.[11,12] Studies to date have inadequately elucidated the disposition and mechanism of action of bretylium. Similarly, the onset and time course of antiarrhythmic effect, blood distribution and elimination kinetics and tissue kinetics have not been well defined. A reliable assay for bretylium to allow such studies has heretofore not been available, and a therapeutic range for drug concentrations has not been established.

Recently, a sensitive and reliable gas chromatographic assay for bretylium was developed in our laboratory,[13] which has allowed us to examine several of these questions about the drug's action. Specifically, our purpose was to investigate the time course of antifibrillatory effects of bretylium after bolus injection in dogs, and to correlate the drug's antiarrhythmic effects with both serum and myocardial concentrations. The results confirm the marked antifibrillatory effect of this agent and emphasize the importance of tissue kinetics in determining this behavior.

Methods

Serum and tissue pharmacokinetic studies in open chest dogs: Ten male mongrel dogs weighing 10 to 20 kg were anesthetized with sodium pentobarbital, 30 mg/kg bodyweight intravenously. The left common carotid artery was exposed and cannulated for continuous monitoring of blood pressure. The left external jugular vein was cannulated as an access route for administration of bretylium tosylate. The right femoral vein was also cannulated, and a catheter placed into the inferior vena cava above the level of the renal veins and below the level of the hepatic veins. Percutaneous electrode leads were attached to generate an electrocardiogram for continuous monitoring. The chest was opened with cautery in the fourth left intercostal space and the heart was suspended in a pericardial cradle.

Bretylium tosylate was administered intravenously over 60 seconds in doses of 6 mg/kg (seven dogs) or 2 mg/kg (three dogs). Blood samples (3 ml) were taken for serum bretylium determinations at the following times after injection: 0, 1, 2, 4, 8, 15 and 30 minutes and 1, 2, 4, 8 and 12 hours. Full thickness myocardial tissue samples (50 to 100 mg) were taken with a cylindrical biopsy punch (4 mm in diameter) from the left ventricular free wall at 30 minutes, 90 minutes, 6 hours and 12 hours after drug injection. The dogs were killed at 12 hours, and tissue samples from the left and right ventricles, interventricular septum, anteromedial papillary muscle, mitral valve and atria were taken immediately post mortem for analysis of cardiac distribution of bretylium. Tissue samples were carefully blotted dry, weighed and dissolved in 500 μliters of 16 normal sodium hydroxide. Solutions were neutralized with 800 μliters of 7 normal hydrochloric acid. Solubilized tissue and serum were analyzed for bretylium concentrations using a high resolution gas chromatographic assay recently developed in this laboratory, and sensitive to 1 ng/ml bretylium.[13] Samples were analyzed in duplicate or triplicate and results expressed as μg/ml or μg/g of bretylium free base in serum or tissue, respectively.

Long-term single dose drug kinetics in closed chest dogs: To determine pharmacokinetics in tissue and serum of single dose bretylium in intact animals, six male mongrel dogs weighing 10 to 20 kg were given a single dose of 6 mg/kg of bretylium tosylate intravenously and observed for 48 to 96 hours (median 72 hours). Using a clean surgical technique, we exposed and cannulated the right internal jugular vein with a 9 French catheter introduced while the animal was sedated with sodium pentobarbital (30 mg/kg). Continuous electrocardiographic monitoring (lead II) was used during drug administration and sampling.

The drug was next administered over 60 seconds. Cardiac tissue samples were taken from the right interventricular septum using the Stanford right ventricular bioptome as described by Mason[14] and adapted to dogs. Three to five individual biopsy specimens were taken at each time point, to yield at least 5 mg of myocardial tissue per sample time. Simultaneously, venous blood (3 to 4 ml) was withdrawn for drug assay. After drug injection, tissue and blood samplings were performed at 30 minutes and 3, 6, 12, 24, 36, 48 and 72 hours.

After initial sampling, the dogs were allowed to recover from pentobarbital anesthesia, then reanesthetized lightly each 12 to 24 hours to provide sufficient sedation for subsequent biopsy samplings. Between sampling times, dogs were fed and watered, and allowed free activity in their cages. After the final sampling point, they were killed and tissue samples from the representative myocardial sites earlier noted were taken for confirmation of final myocardial drug concentration and intracardiac distribution of drug. Samples were processed and analyzed as previously described.

Ventricular fibrillation threshold determination: To determine the effect of bretylium on the ventricular fibrillation threshold, 17 male mongrel dogs weighing 10 to 20 kg were given bretylium intravenously in doses of 2 mg/kg (6 dogs) or 6 mg/kg (4 dogs) of the tosylate salt or normal saline solution (7 dogs) over 60 seconds. Serial determinations of the ventricular fibrillation threshold were made.[15,16] Dogs were prepared while sedated with sodium pentobarbital (30 mg/kg). The common carotid artery was isolated and cannulated for constant arterial pressure monitoring using a Statham pressure transducer. The left external jugular vein was cannulated as a venous access site for drug administration. With use of cautery, a left thoracotomy was performed in the fourth intercostal space and the heart was suspended in a pericardial cradle.

A biopolar electrode, consisting of silver-silver chloride electrodes 1 mm in diameter and imbedded in an acrylic plaque, was sewn onto the anterior right ventricle. Electrodes were cleaned daily with emery paper. A pacing electrode was attached to the left atrium using an alligator clip to allow for pacing with a Grass model SD5 stimulator. A plunge bipolar electrode (1 cm in length) was sewn into the surface of the left

ventricle and used to determine the effective refractory period. Lead II of the electrocardiogram was monitored continuously on a Tektronix oscilloscope. The left anterior descending coronary artery was dissected free in its mid portion. A double ligature was passed under the artery and the vessel was temporarily occluded for 2 minutes for the determination of thresholds during ischemia, as noted later. Ventricular effective refractory periods, ventricular fibrillation thresholds (without and with ischemia) and repetitive ventricular response thresholds were all measured in the same series of dogs.

Determination of ventricular fibrillation threshold was performed with a modification of the method of Kroll and Lucchesi.[16] Animals were paced from the atrium at 175 beats/min. Four ms fibrillation pulses of 60 hertz frequency and 200 ms total duration were synchronized to the pacing stimulus with a 50 ms delay, so as to scan the T wave in the vulnerable period of the heart. The current delivered was measured exactly by recording voltage drop across a precision 1,000 ohm resistor in series with the electrodes. Current intensity was increased in 0.5 mA increments to 5 mA, then in 1 mA increments to 10 mA, 2 mA increments to 20 mA and 5 mA increments to 50 mA until ventricular fibrillation developed. Three attempts at each current level were made. The current intensity inducing sustained ventricular fibrillation was defined as the ventricular fibrillation threshold. When fibrillation occurred, the heart was immediately defibrillated using a capacitor discharge direct current defibrillator charged to 10 to 15 joules. The heart was allowed to recover for a minimum of 15 minutes after each determination.

The schedule for determination of ventricular fibrillation threshold was as follows: Before drug administration, a control determination was made in the absence of ischemia. After a 15 minute rest interval, the mid anterior descending coronary artery was ligated and control ischemia threshold determinations were begun after 2 minutes. The ligature was released after fibrillation was precipitated, and the heart was promptly defibrillated. A 30 minute recovery period was allowed and drug or saline solution was administered. Two minutes after injection the threshold was determined; 30 minutes after the drug was given, threshold measurements were repeated; a 15 minute interval was allowed and ischemic threshold was determined. Similar threshold determinations without and with ischemia were made at 90 minutes and 3, 6 and 12 hours after injection. Adequate hydration was provided to maintain blood pressure in the normal range over the 12 hour period of study.

Ventricular effective refractory period and response threshold: Ventricular response threshold was measured at the beginning of each determination of ventricular fibrillation threshold. The ventricular response threshold was defined as the minimal current required to induce a ventricular premature beat in one to three attempts.

The left ventricular effective refractory period was defined as the longest Q-S_2 interval at which a premature impulse (Q-S_2) consistently failed to cause ventricular depolarization; this refractory period was assessed just before each determination of ventricular fibrillation threshold. To make this determination, ventricular extrastimuli (S_2) were introduced after every eight paced sinus beats at two to three times diastolic threshold through a plunge bipolar electrode in the left ventricle. Q-S_2 intervals were reduced by 5 to 10 ms until ventricular capture failed.

Repetitive ventricular response threshold: During the determinations of ventricular fibrillation threshold, the current at which more than two premature complexes were elicited by the fibrillation pulse (during at least one of three trials at a given current level) was defined for purposes of this study as the repetitive ventricular response threshold.

Three to four ml of blood was withdrawn at the time of each threshold determination, to enable comparisons to be made between serum bretylium concentrations and drug effects. Samples were obtained at 2, 30 and 90 minutes and 3, 6 and 12 hours, and analyzed as previously described. Immediately after testing at 12 hours, the animal was killed and a 1 g tissue sample obtained from the left ventricle. Tissue analysis for bretylium was performed as previously noted.

Analysis of data: Electrophysiologic variables and serum and tissue drug concentrations were plotted as mean ± standard error of the mean versus time for each separate group of animals. Drug elimination constants were determined by a linear regression program. Differences in mean responses of two or three groups at a given time were analyzed with Student's *t* test or with analysis of variance for pairwise comparisons.[17] When geometric response in the group receiving 6 mg/kg substantially violated the equal variance assumption (that is, repetitive ventricular response threshold, nonischemic dogs), treatment responses were analyzed independently with use of the *t* test. Paired *t* testing was used to compare response of a given variable in animals under two conditions. Similarity in response of different variables at a given time was sought using a correlation program. Significance was assumed at a probability (p) level of <0.05. For purposes of analysis, a (minimal) ventricular fibrillation threshold of 50 mA was

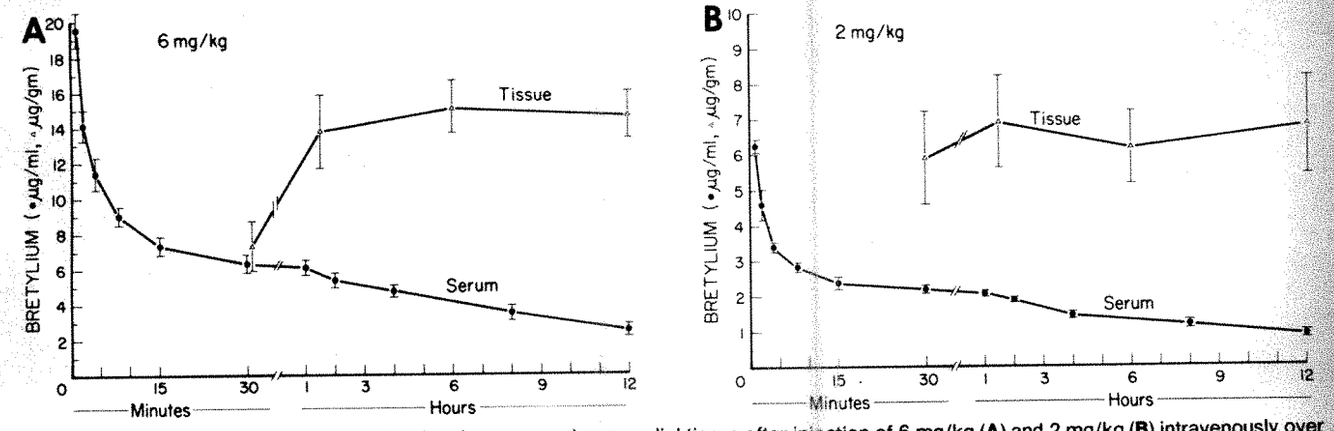


FIGURE 1. Concentrations of bretylium tosylate in serum and myocardial tissue after injection of 6 mg/kg (**A**) and 2 mg/kg (**B**) intravenously over 60 seconds in open chest dogs (seven and three dogs, respectively). Results given as mean ± standard error of the mean.

assigned in instances where the measureable threshold was exceeded.

Results

Serum and tissue bretylium in open chest dogs: After intravenous injection of 6 mg/kg (n = 7) of bretylium tosylate, in seven open chest dogs serum bretylium concentration decreased rapidly along a curvilinear (biexponential) curve from a peak of 19.6 ± 1.1 μg/ml, at 1 minute after injection, to 6.5 ± 0.4 μg/ml at 30 minutes and 2.5 ± 0.3 μg/ml at 12 hours (Fig. 1A). Distribution half-life (t 1/2) was approximately 3 minutes and terminal t 1/2 9.1 hours. Myocardial drug concentration, in contrast, increased progressively with respect to serum drug concentration over the 12 hour period. Tissue bretylium was similar to serum bretylium at 30 minutes (7.3 ± 1.4 μg/g), increased rapidly by 90 minutes (13.7 ± 1.2 μg/g), peaked by 6 hours (15.1 ± 1.5 μg/g) and remained at a plateau elevation at 12 hours (14.6 ± 1.3 μg/g). The ratio of myocardial to serum bretylium increased progressively throughout the study to 1.2 ± 0.3 by 30 minutes and to 6.4 ± 1.0 at 12 hours.

The cardiac distribution of bretylium is shown in Figure 2. At 12 hours significant correlations existed in bretylium concentrations in the left ventricle (14.6 ± 1.3 μg/g), right ventricle (14.3 ± 1.5 μg/g), interventricular septum (14.6 ± 1.6 μg/g) and anteromedial papillary muscle (14.0 ± 1.6 μg/g; $p < 0.01$ for all correlations). Atrial bretylium concentration was slightly although significantly lower (12.2 ± 1.2 μg/g; correlation $p > 0.05$). In contrast, the mitral valve leaflet, a relatively avascular tissue, accumulated bretylium to a concentration of only 2.0 ± 0.3 μg/g.

After injection of 2 mg/kg of bretylium tosylate (three dogs), serum bretylium concentration decreased along a multiphasic curve similar to that for the larger dose (Fig. 1B). Serum bretylium declined from 6.25 ± 0.14 μg/ml at 1 minute after injection to 2.19 ± 0.08 μg/ml at 30 minutes and to 0.87 ± 0.10 μg/ml at 12 hours. Myocardium concentrated bretylium heavily at this dose as well, with tissue bretylium maintaining a plateau of nearly 7 μg/g between 90 minutes and 12 hours. A progressive increase in the ratio was 8.5 ± 2.8.

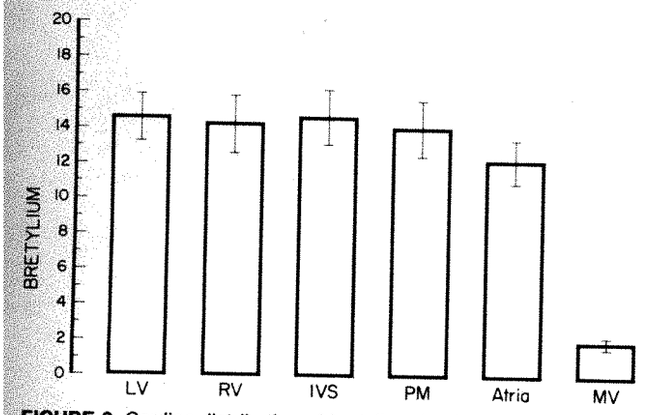


FIGURE 2. Cardiac distribution of bretylium (μg/g) at 12 hours in the seven dogs in Figure 1A. IVS = interventricular septum; LV = left ventricle; MV = mitral valve leaflet tissue; PM = anteromedial papillary muscle; RV = right ventricle. Results given as mean ± standard error of the mean.

Long-term serum and tissue bretylium in closed chest dogs: Serum and myocardial bretylium concentrations measured in closed chest dogs allowed to recover consciousness are presented in Figure 3. Myocardial tissue was obtained by transvenous endomyocardial biopsy from the right interventricular septum in six dogs at various time points after 6 mg/kg of bretylium was injected (see methods). The accuracy of measurements obtained with endomyocardial biopsy samples was confirmed by comparison with larger samples obtained when the dogs were killed. Serum and cardiac bretylium concentrations were similar at 30 minutes (7.15 ± 0.59 and 7.85 ± 0.68 μg/mg, respectively), with a mean tissue to serum ratio of 1.2 ± 0.1. These measurements were also similar to those at 30 minutes in closed chest dogs (Fig. 1A). Serum bretylium then continued to decrease in a nonlinear exponential fashion to 1.35 ± 0.07 μg/ml at 12 hours. This somewhat smaller concentration, when compared with the 12 hour value in open chest given bretylium on a short-term basis, may reflect improved renal excretion in these lightly anesthetized intact animals. Between 12 to 24 and 72 hours, elimination followed a log-linear course, with an elimination rate constant (λ1-s) by linear regression analysis of 0.0663 ± 0.008 $hour^{-1}$, and an elimination half-life from serum (t 1/2-s) of 10.4 hours (harmonic mean).

Myocardial bretylium concentration increased after 30 minutes to peak levels at 3 and 6 hours of 11.3 ± 0.7 and 13.0 ± 2.3 μg/g, respectively. Myocardial concentration of the drug persisted at this high level until 12 hours (11.2 ± 1.6 μg/g), then decreased in parallel with serum bretylium concentration between 24 and 72 hours from 6.25 ± 0.91 to 0.37 ± 0.05 μg/g. Tissue elimination rate constant (λ1-m) between 24 and 72 hours was 0.0662 ± 0.009 $hour^{-1}$, virtually identical to that for serum (λ1-s). Myocardial elimination half-life (t 1/2-m) was 10.5 hours. The ratio of myocardial to serum bretylium in this interval averaged 12.6 ± 1.9 μg/g per μg/ml in the six dogs. These data indicate, in the intact animal, marked myocardial concentration of bretylium, with pseudoequilibrium (parallel elimination) being first established between 12 and 24 hours after single dose injection. Myocardial bretylium was still easily detectable by our assay at 72 hours.

Effects on effective refractory period and response threshold: Bretylium injections caused a time-dependent increase in the left ventricular effective refractory period (Fig. 4). The effective refractory period was unaffected by determination of the ventricular fibrillation threshold, including cardioversion, as shown by the comparability of refractory periods before and after control fibrillation threshold measurement in each group (p = difference not significant). Each of the two control refractory period measurements were also comparable among the three groups. However, after injection of bretylium, significant divergence in response among treated and control groups developed by 90 minutes ($p = 0.007$) and persisted through 12 hours

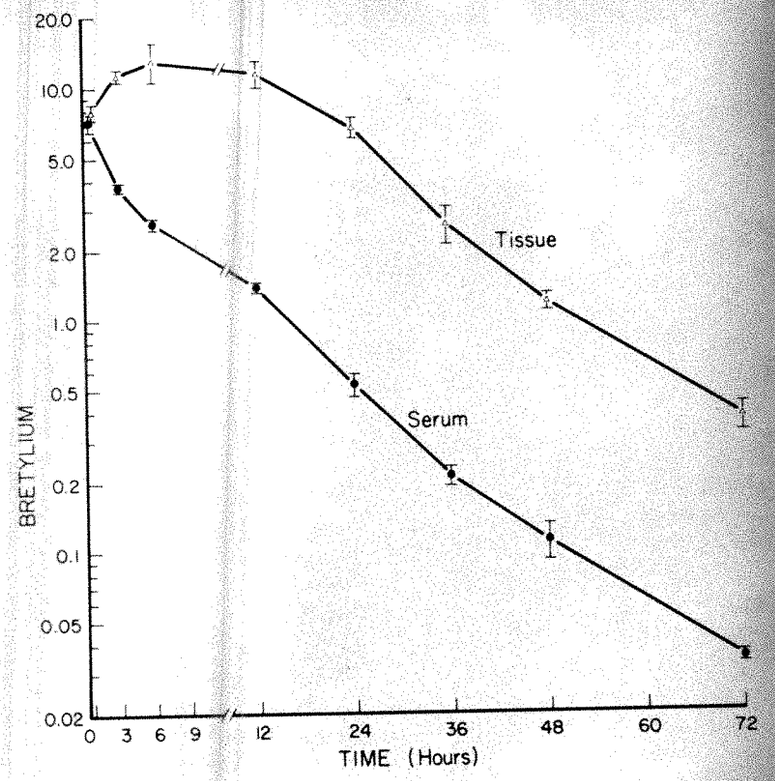


FIGURE 3. Bretylium concentrations in serum (μg/ml) and myocardial tissue (μg/g) in closed chest dogs after bolus injection of 6 mg/kg of the drug. Tissue samples obtained by transvenous endomyocardial biopsy. All six dogs were observed for 48 hours, three for 72 hours and one for 96 hours (point not shown). Values plotted as mean ± standard error of the mean.

($p = 0.046$, analysis of variance). Response after injection of saline solution was flat over time, with mean effective refractory periods of 151 to 153 ms. In contrast, after administration of 6 mg/kg of the drug (four dogs), the refractory period increased from 156 ± 3 at 0 minute and 158 ± 1 at 30 minutes to 171 ± 4 ms at 90 minutes. The peak effective refractory period obtained at 3 hours (177 ± 3 ms) persisted at 6 hours (174 ± 4 ms) and declined (to 164 ± 4 ms) by 12 hours. Increases after administration of 2 mg/kg of the drug (six dogs) were slightly but not significantly less than those after 6 mg/kg, but were significantly greater (90 minutes to 6 hours) than those after administration of saline solution (Scheffe).

Control ventricular response threshold averaged 0.11 ± 0.01 mA (16 dogs), and varied in a fashion similar to effective refractory period. The response threshold was invariant after fibrillation threshold determinations and over the 12 hour study period after injection of saline solution, but tended to increase after administration of bretylium. The peak response threshold occurred at 6 hours, averaging 0.17 ± 0.02 mA after 2 mg/kg and 0.18 ± 0.03 after 6 mg/kg of the drug was given. These changes were not quite significant ($p = 0.05$ to 0.10).

Effects on ventricular fibrillation threshold: Marked increases in ventricular fibrillation threshold developed after injection of bretylium tosylate (Fig. 5). Differences in response among the groups treated with bretylium and the control group treated with saline solution were obviously highly significant from 2 minutes to 12 hours ($p < 0.001$, analysis of variance) (Table I).

At 2 minutes after injection of 6 mg/kg of the drug (nonischemic conditions), ventricular fibrillation could be elicited in two dogs (at 35 mA and 40 mA, respectively) but not in another two dogs (greater than 50 mA) ($p = 0.002$, control time versus 2 minutes). Complete protection from ventricular fibrillation at 50 mA continued thereafter throughout 12 hours of observation in the nonischemic state in all four animals. With 2 minutes of coronary ischemia, the heart of one of four

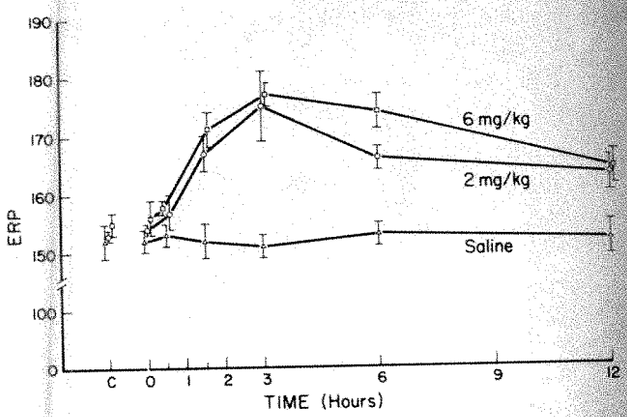


FIGURE 4. Effective refractory period (ERP) plotted in ms ± standard error of the mean versus time. Control time C is before drug administration and initial ventricular fibrillation threshold determination. Control time 0 is after initial determination of fibrillation threshold and directly before drug administration. Other times are 2, 30 and 90 minutes and 3, 6 and 12 hours. Groups include four dogs receiving 6 mg/kg of bretylium, six receiving 2 mg/kg and six receiving saline solution.

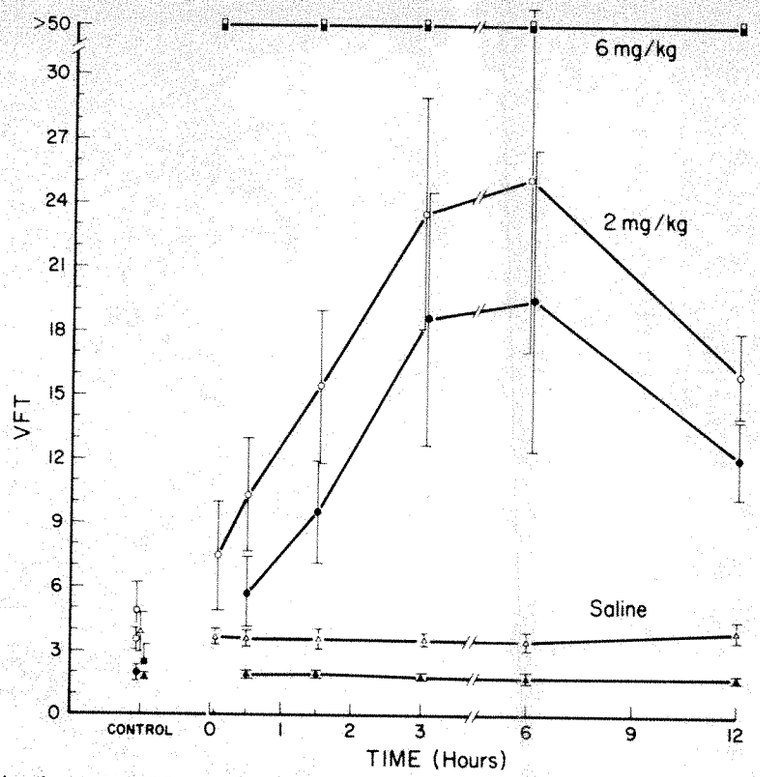


FIGURE 5. Ventricular fibrillation threshold (VFT) response in mA with time after acute injection of 6 mg/kg (four dogs) or 2 mg/kg (six dogs) of bretylium or of saline solution (six dogs). **Open symbols** represent nonischemic and **closed symbols** represent ischemic (2 minutes) conditions (see text). Values are plotted as mean ± standard error of the mean. The control measurement is before drug administration; first measurement after drug administration is at 2 minutes (nonischemic). The mean ventricular fibrillation threshold for the group receiving bretylium is greater than 50 mA, which is above the range of determination. See text for individual variations.

TABLE I

Ventricular Fibrillation Threshold (mA) Without and With Ischemia*

Dog	Control (0)	2 min	30 min	90 min	3 h	6 h	12 h
			Group I (saline-treated control group)				
1	3.0/2.0	3.5/—	3.0/2.5	3.5/2.0	3.5/2.5	3.5/2.0	3.5/2.0
2	4.5/2.0	4.0/—	4.0/2.5	5.0/3.0	4.0/2.0	3.5/1.5	6/2.5
3	2.0/2.0	2.5/—	2.0/2.0	2.0/1.5	2.5/2.0	2.0/2.0	2.5/2.0
4	3.5/1.0	4.0/—	4.5/1.0	3.0/1.0	3.5/1.0	3.0/1.0	3.5/1.0
5	4.0/1.5	3.5/—	3.5/1.5	3.5/1.5	4.0/1.5	4.0/1.5	4.0/1.5
6	4.5/1.5	4.5/—	4.5/2.0	4.5/2.0	4.0/1.5	5.0/2.0	4.5/2.0
Mean (Dogs 1–6) ± SEM (NI/I)	3.6 ± 0.4/ 1.7 ± 0.2	3.7 ± 0.4/ —	3.6 ± 0.4/ 1.9 ± 0.2	3.6 ± 0.5/ 1.8 ± 0.3	3.6 ± 0.2/ 1.8 ± 0.2	3.5 ± 0.4/ 1.7 ± 0.2	4.0 ± 0.5/ 1.8 ± 0.2
			Group II (small dose [2 mg/kg] bretylium-treated)				
7	2.5/2.5	2.0/—	1.5/3.0	2.5/2.5	3.0/4.5	5.0/4.5	16/12
8	2.0/1.0	1.5/—	4.5/3.0	9/8	18/16	20/16	16/12
9	4.0/2.0	4.5/—	16/2.0	18/4.5	40/45	>50/>50	20/16
10	5.0/3.5	18/—	16/12	22/18	25/20	20/16	18/12
11	4.0/2.0	9/—	8/4.0	16/10	20/8	10/6	6/4.0
12	4.0/1.5	10/—	16/10	25/14	35/18	35/25	20/16
Mean (Dogs 7–12) ± SEM (NI/I)	3.6 ± 0.5/ 2.1 ± 0.4	7.5 ± 2.5/ —	1.3 ± 2.7/ 5.7 ± 1.7	15.5 ± 3.4/ 9.5 ± 2.4	23.5 ± 5.4/ 18.6 ± 5.8	25.0 ± 8.2/ 21.3 ± 8.3	16.0 ± 2.1/ 12.0 ± 4.4
			Group III (large dose [6 mg/kg] bretylium-treated)				
13	9/5.0	>50/—	>50/>50	>50/>50	>50/>50	>50/>50	>50/>50
14	3.0/1.5	>50/—	>50/18	>50/>50	>50/>50	>50/>50	>50/40
15	4.0/2.0	35/—	>50/>50	>50/>50	>50/>50	>50/>50	>50/35
16	3.0/1.5	40/—	>50/>50	>50/>50	>50/>50	>50/>50	>50/>50
Mean (Dogs 13–16) ± SEM (NI/I)	4.8 ± 1.4/ 2.5 ± 0.8	>50/—	>50/≥50	>50/>50	>50/>50	>50/>50	>50/≥50

* Individual ventricular fibrillation threshold response is given in milliamperes (mA) at times indicated after drug or saline injection for dogs in groups I to III. For each time, the number to the left of the slash indicates the value without ischemia (NI) and the number to the right of the slash indicates the value after 2 minutes of coronary ischemia (I) (that is, nonischemic/ischemic).

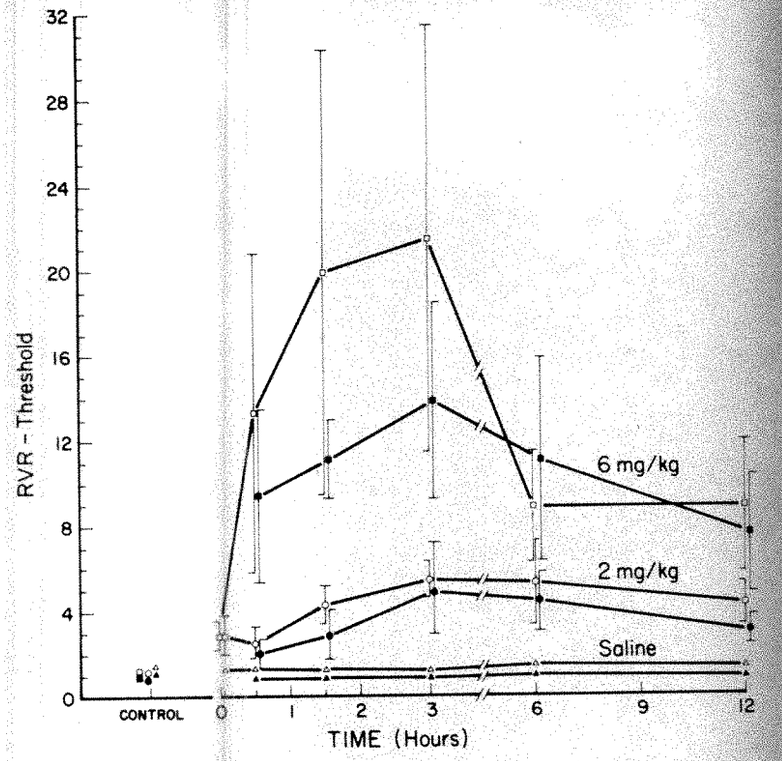


FIGURE 6. Repetitive ventricular response (RVR) threshold (mA) versus time before (control) and after administration of drug or saline solution. Times and number are similar to those in Figure 5. Results are plotted as mean ± standard error of the mean. **Open symbols** indicate nonischemic, **closed symbols** ischemic (2 minutes) conditions. The first measurement after drug administration is at 2 minutes (nonischemic).

dogs could be fibrillated at 30 minutes (at 18 mA); ($p = 0.002$, control time versus 2 minutes) and that of two of four at 12 hours (at 35 mA and 40 mA). For all other determinations, protection from fibrillation despite ischemia was provided to the maximal level, 50 mA impulses.

Increases in ventricular fibrillation threshold also occurred after injection of 2 mg/kg of bretylium salt (six dogs), but these changes fell within the range of determination (Fig. 5). By 2 minutes after-injection, fibrillation threshold had increased from 3.6 ± 0.5 to 7.5 ± 2.5 mA, and by 30 minutes to 10.3 ± 2.7 mA, significantly above control time ($p = 0.03$). The threshold continued to rise in a linear manner to peak at 3 hours (at 23.5 ± 5.4 mA) and 6 hours (25.0 ± 8.2 mA), and decreased somewhat by 12 hours (to 16.0 ± 2.1 mA). Differences between groups treated with bretylium and the group treated with saline solution were apparent from 90 minutes through 12 hours (Scheffe).

The ventricular fibrillation threshold response was similar after ischemia at each time point in the group receiving 2 mg/kg, but thresholds were lower than for nonischemic conditions (Fig. 5). As noted in Methods, each animal served as its own control for ischemic versus nonischemic conditions. The mean threshold during control determination was 2.1 ± 0.4 mA, increased to 5.7 ± 1.7 mA at 30 minutes after drug administration ($p = 0.03$) and further increased to maximal levels at 3 and 6 hours (18.6 ± 5.8 mA, 21.3 ± 8.3 mA, respectively). Some decrease occurred by 12 hours (to 12.0 ± 1.8 mA). Differences between the bretylium-treated and saline-treated groups were significant from 30 minutes to 12 hours ($p < 0.01$, Scheffe).

No change occurred in the fibrillation threshold of the seven control animals receiving saline solution with time in either the ischemic or nonischemic state. This response in control animals verifies the stability of ventricular fibrillation threshold over at least 12 hours in these open chest preparations. The threshold with ischemia (1.7 to 1.9 mA, range of the mean) was approximately half of that without ischemia (3.5 to 4.0 mA, range of the mean) and differed significantly at each timed determination (t test). This finding confirms the deleterious effect of ischemia on ventricular fibrillation threshold.

Effects on repetitive ventricular response threshold: The effect of bretylium on the repetitive ventricular response threshold as defined in Methods is shown in Figure 6. After injection 6 mg/kg of bretylium tosylate in four dogs, the mean response threshold began to increase by 2 minutes (from 1.3 ± 0.3 to 2.8 ± 0.9 mA), peaked at 3 hours (21.4 ± 10.0 mA), then decreased but remained elevated above control values at 12 hours (8.8 ± 3.2 mA). Significant geometric differences between the bretylium-treated and saline-treated groups were present between 30 minutes and 12 hours ($p < 0.003$, t test). After 2 minutes of coronary ischemia, 6 mg/kg of the drug also raised the response threshold so that at 90 minutes it had increased from 1.3 ± 0.4 to 11.1 ± 3.7 mA ($p = 0.01$). The bretylium-treated and saline-treated groups showed differences between 30 minutes and 12 hours (t test). As expected, the absolute elevation during ischemia was generally lower than during nonischemic conditions.

Elevation in repetitive ventricular response threshold of a lower magnitude developed after 2

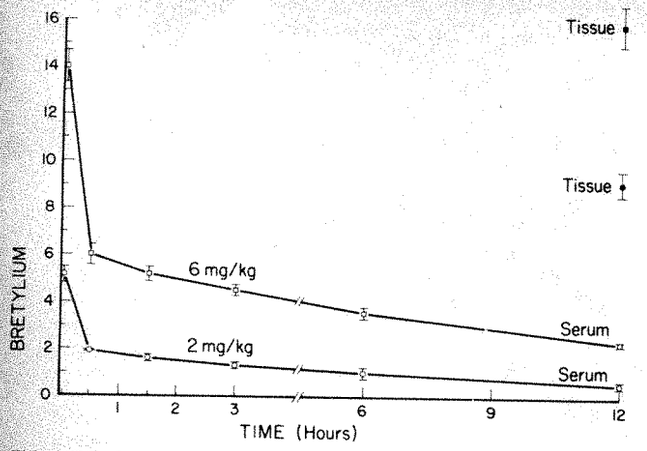


FIGURE 7. Serum (μg/ml) and final myocardial tissue (μg/g) concentrations of bretylium in animals subjected to electrophysiologic testing (Fig. 4 to 6). Results are presented as mean ± standard error of the mean. Compare also with Fig. 1, A and B.

mg/kg of bretylium tosylate. In this group (n = 6) the threshold increased from 1.2 ± 0.2 mA in the control period to 4.0 ± 1.1 mA at 90 minutes (p = 0.03), and to a maximum of 5.4 ± 1.9 mA at 3 hours. Persistent elevation of 4.3 ± 1.0 mA was present at 12 hours. The bretylium-treated and saline-treated groups showed significant differences between 90 minutes and 12 hours (*t* test). Similarly, augmentation in the response threshold occurred in animals treated with 2 mg/kg of the drug after coronary ischemia, with control threshold of 0.8 ± 0.2 mA rising significantly to 2.0 ± 0.6 at 30 minutes (p = 0.03), and further to 4.9 ± 2.0 mA at 3 hours. Elevation persisted at 12 hours (3.0 ± 0.6 mA). The mean values in the saline- and bretylium-treated groups were significantly different from 90 minutes to 12 hours.

The repetitive ventricular response threshold was stable for 12 hours in the control animals injected with saline solution. Repetitive response was elicited at lower current with ischemia (mean 0.7 ± 0.1 mA) than without ischemia (1.5 ± 0.1 mA) (p = 0.03, *t* = 0) (Fig. 6).

Previously proposed as a subfibrillatory measure of ventricular fibrillation threshold, repetitive ventricular response threshold followed the general temporal configuration of fibrillation threshold, although at approximately one fourth the current level. The repetitive response data also suggest a proportionate three- to four-fold greater effect of the three-fold greater dose of bretylium salt (6 mg/kg versus 2 mg/kg). However, in contrast to mean results, the relation of repetitive ventricular response and ventricular fibrillation thresholds in individual animals was too variable to be of much predictive value. Only at 30 and 90 minutes with ischemia (in animals receiving 2 mg/kg) was there an individual correlation of these two thresholds (p = 0.05).

Serum and tissue bretylium in animals tested for ventricular fibrillation threshold: Serial serum concentrations of bretylium measured at the time of ventricular fibrillation threshold determinations for the four animals receiving 6 mg/kg and the six animals receiving 2 mg/kg of the drug are presented in Figure 7. In addition, myocardial (left ventricular) bretylium concentrations at the time the dogs were killed (12 hours) are shown. There is no significant difference between these serum concentration curves and those presented in Figure 1 for the tissue pharmacokinetic study. Tissue levels at 12 hours were likewise similar. Once again, the mean final (12 hour) tissue to serum ratio was greater for the group receiving 2 mg/kg than for the group receiving 6 mg/kg (17.9 ± 3.9 versus 6.9 ± 1.8). It may thus be presumed that the detailed tissue kinetics determined as in Figure 1 apply to the group subjected to ventricular fibrillation threshold determinations.

As expected, a variable (usually modest) increase in blood pressure and heart rate occurred seconds to minutes after drug administration. In all cases, these changes had returned to baseline within 30 minutes. The kinetics of ventricular fibrillation threshold elevation were thus distinct from those of the catecholamine release reaction.

Discussion

Role of myocardial drug concentration in determining therapeutic effects: These kinetic studies emphasize the importance of drug concentrations at tissue sites of action in myocardium in determining therapeutic effects. Whereas serum bretylium concentration decreased rapidly after intravenous injection, both myocardial bretylium concentration and antifibrillatory and electrophysiologic effects increased gradually, peaking at approximately 3 hours. These kinetic results were similar with or without myocardial ischemia and for both doses of bretylium. Bretylium was heavily concentrated in myocardial tissue (6 to 18-fold), suggesting that small changes in serum bretylium at equilibrium might be associated with wide and variable swings in tissue concentration. In addition, conditions of pseudoequilibrium (parallel elimination) in tissue and serum compartments were not obtained until 12 to 24 hours after short-term dosing, as demonstrated in the 72 hour dog model with subsequent elimination half-life in tissue and serum of 10.5 hours. In summary, serum bretylium concentrations after short-term dosing are not predictive of drug effects, whereas an understanding of tissue drug kinetics and concentrations appears to be very useful.

Effect of bretylium on ventricular fibrillation threshold: Bretylium caused marked increases in ventricular fibrillation threshold, confirming its reported efficacy as an antifibrillatory agent.[15,18–20] The canine model used confirms the deleterious effect of ischemia on fibrillation threshold[21] and documents a relatively equipotent therapeutic effect in the ischemic and the nonischemic heart. The responses observed suggest incremental effects on fibrillation threshold of increasing doses of bretylium, in the range tested. Our canine preparation proved to be a highly stable model for threshold determinations over the 12 hour period of observation.

The repetitive ventricular response threshold was a useful predictor of group response of ventricular fibrillation threshold to drug. However, in the individual animal, the correlation was too variable to be useful. In general, at least a proportionate rise in antiarrhythmic effect is predicted by the repetitive ventricular response as the dose is increased from 2 to 6 mg/kg. The data on repetitive ventricular response also suggest that peak drug effect after 6 mg/kg, similar to that of a smaller dose, occurs at approximately 3 hours.

The time course of change in effective refractory period was similar to that for ventricular fibrillation and repetitive response thresholds. However, increases in refractory period were not proportionate to increases in drug concentration. The parallel temporal change of effective refractory period and fibrillation threshold suggests a correlation between drug effect on effective refractory period and on fibrillation threshold. On the other hand, incremental change in refractory period using 6 mg/kg in comparison with 2 mg/kg was much less than that for fibrillation threshold. These observations suggest a nonlinear relation between these two measures of drug effect or the importance of factors in addition to changes in refractory period in determining ventricular fibrillation threshold.

These studies demonstrate the utility of endomyocardial biopsy in allowing long-term observations of drug kinetics in myocardial tissue. Information derived may be particularly useful for clinical comparisons. Our observations confirmed the long persistence of drug in myocardium after single dosing, with detectable drug persisting for more than 72 to 96 hours.

Mechanism of bretylium's cardiac effects: Controversy continues to exist as to whether bretylium has important direct effects on the human heart independent of its action on the adrenergic neuron.[3,4] Experimental work suggests that both direct electrophysiologic effects and myocardial concentration of drug are independent of cardiac nerves.[8,22,23] Cardinal and Sasyniuk[9] showed that bretylium increases action potential and refractory period duration in isolated Purkinje fibers, and reduces the disparity in local action potential duration between normal and infarct preparations. Namm et al.,[22] using immunosympathectomized rats, showed the marked myocardial concentrations of bretylium to be independent of cardiac sympathetic nerve uptake. Electrophysiologic effects, including lengthening of effective refractory period and action potential duration, were also similar in both normal and immunosympathectomized animals. Bretylium was found to bind to cell plasma membranes in a tight but reversible fashion. Our observations lend support to those of these workers, and suggest that the kinetics of electrophysiologic and antifibrillatory effects of bretylium parallel those of drug accumulation in myocardial tissue. In contrast, the kinetics of catecholamine release and serum drug are dissimilar.

Serum versus myocardial drug kinetics: Detailed studies of myocardial tissue kinetics of other antiarrhythmic drugs have not come to our attention. The relation between serum drug kinetics and drug action after short-term administration varies among these agents. With drugs such as lidocaine, a direct temporal relation appears to exist. Schnittger et al.[24] demonstrated a linear relation between plasma lidocaine concentrations during acute infusions and increases in ventricular fibrillation threshold. With other drugs such as bretylium, acute effects are dissociated from blood kinetics and maximal effects may be substantially delayed. The antiarrhythmic effect of amiodarone does not become evident until 4 to 8 days after therapy is begun.[25] Intravenous propranolol may yield immediate therapeutic benefit, but plasma concentrations do not correlate simply with drug effects.[25] Lameijer and van Zweiten[27] found slow (1 to 3 hours), 10-fold concentration of quinidine in the isolated mammalian heart and parallel temporal changes in refractory period. Strauss et al.[28] found procainamide to be concentrated in myocardium in a ratio of 2.3:1, after a 4 hour loading infusion, but kinetics were not studied. Further studies of myocardial tissue kinetics of these drugs would be of interest.

Clinical implications: Our study in dogs demonstrates marked time- and dose-dependent differences in response to bretylium tosylate. Clinical extrapolation of these data as in other animal studies must be tentative. However, clinical implications might include the need for repeated acute drug dosing and allowance of greater time after acute bretylium administration before assuming drug failure. Current package insert recommendations reflect this implication.[29] Thus, if the initial 5 mg/kg bolus injection of bretylium is ineffective in restoring rhythm, additional dosing up to 30 mg/kg total over about 30 minutes is suggested.[29] The delayed response in ventricular fibrillation threshold rise seen with our small dose might thereby be converted to an immediate response similar to that seen with our larger dose (Fig. 5). This study confirms the utility and sensitivity of a new drug assay for bretylium using a gas recently described chromatographic method.[13] A more rational approach to administration of bretylium in patients should result from clinical application of this assay and further testing of the inferences suggested by this study.

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Myocardial Effects of Long-Term Cigarette Smoking: Relative Roles of Carbon Monoxide and Nicotine

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In a prior study of an animal model exposed to long-term cigarette smoking, left ventricular performance was observed to decline in association with morphologic evidence of collagen accumulation. Because controversy has existed as to whether nicotine or carbon monoxide is the major pathogenetic agent in cigarette smoking, 18 young adult male beagles with chronic tracheostomy were placed in three groups of six dogs each: Group 1 served as a control group; group 2 received seven cigarettes of low nicotine content (0.2 mg/cigarette), which effected a peak carboxyhemoglobin level approximating 5/100 ml, similar to that of regular cigarettes; and group 3 received nicotine twice daily intramuscularly in an amount equivalent to seven cigarettes/day. In the intact anesthetized state, heart rate, left ventricular end-diastolic pressure and volume (indicator dilution) did not differ among the three groups. To assess relative myocardial wall stiffness, saline solution was infused into the left ventricular chamber. A significantly higher end-diastolic pressure and tension were elicited in group 3, suggesting a decrease in left ventricular compliance. No such change was observed in either group 1 or 2. Only long-term nicotine use was associated with increased hydroxyproline content in the left ventricular myocardium, suggesting a basis for enhanced stiffness. An index of left ventricular contractility was derived from the peak rate of rise of left ventricular pressure (dP/dt), normalized for preload and afterload. Groups 1 and 2 showed no difference in this index (2.18 ± 0.3 versus 2.15 ± 0.18 muscle lengths/s per cm) at similar levels of aortic pressure, but the index was significantly lower (1.28 ± 0.12, $p < 0.01$) in group 3. Thus, the effects of long-term cigarette use on the myocardium appear to be predominantly dependent on nicotine rather than on carbon monoxide.

Although several epidemiologic and pathologic studies[1,2] have suggested an increased incidence of cardiovascular disease among persons who smoke, a direct causal relation between long-term smoking and cardiac disease has not been established. In a previous study of an animal model,[3] the effects of long-term smoking and nicotine administration were observed to produce functional and morphologic abnormalities of the left ventricle consistent with the view that habitual smoking has an effect on the myocardium independent of coronary artery disease. The toxic effects of smoking were considered largely dependent on the nicotine content of cigarettes.

Carboxyhemoglobin levels similar to those found in heavy smokers have been reported to accelerate atherosclerotic changes and induce myocardial damage in animals. Carbon monoxide, and not nicotine, was therefore considered the major toxic component responsible for the increased risk of cardiovascular disease.[4] To test the latter assumption this study was undertaken to determine the relative alterations of myocardial function and composition in an animal model as a response to long-term carbon monoxide or nicotine use.

Methods

Experimental preparation: To assess the relative roles of nicotine and carbon monoxide as the major pathogenetic agent in the development of heart muscle disease due to long-term cigarette smoking, 18 month old littermate male beagles were prepared with a permanent tracheostomy. They were alternately placed into three groups of six dogs each: group 1, a control group; group 2, dogs

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smoking daily seven cigarettes with negligible nicotine content; and group 3, dogs receiving intramuscularly doses of nicotine previously shown to mimic the left ventricular responses to cigarette smoking.[3]

Smoking in group 2 was performed by the method of Cahan and Kirnan.[5] The cigarettes were a commercial brand (Sano) without filters and contained only 0.2 mg nicotine/cigarette. The smoking was done in two sessions each day. In group 3 (nicotine users), 210 μg/kg of nicotine was injected intramuscularly twice a day. This dose was considered approximately equivalent to that observed in beagles that have smoked seven cigarettes containing 1.35 mg of nicotine/cigarette.[3]

Body weight, hematocrit, serum proteins and electrolytes were monitored throughout. At the end of the 18 month study, the dogs were anesthetized with morphine sulfate (3 mg/kg body weight) and sodium pentobarbital (15 to 20 mg/kg) 18 hours after eating and were placed in the right lateral position. After insertion of a cuffed endotracheal tube, respiration was regulated with a Harvard respiratory pump. This procedure facilitated the maintenance of arterial pH and partial pressures of oxygen and carbon dioxide in the normal range.[3]

Hemodynamic measurements: For pressure measurements an 80 cm 8F National Institutes of Health catheter was passed through the right carotid artery into the left ventricular chamber. From the left carotid artery, a 55 cm 8F National Institutes of Health catheter was placed in the aortic root, 1 to 2 cm above the aortic valve. A 50 cm 7F Swan-Ganz catheter was passed through the jugular vein into the pulmonary artery and a small polyethylene catheter (PE) into the femoral vein. Statham transducers were used for the measurement of left ventricular (P23Gb) and aortic (P23Db) pressures. These were placed at the mid thoracic level and balanced for equal sensitivity. The maximal rate of rise of left ventricular pressure (dP/dt) was obtained using the resistance-capacitance differentiating circuit. Systolic ejection period was measured from superimposed aortic and left ventricular pressure pulse tracings. The frequency response of this system is linear from 0 to 30 cycles/s. End-diastolic pressure was measured over at least two respiratory cycles and averaged. This measurement has been found to correlate to a high degree with the pressure measurement obtained using a micromanometer tip (Millar®) catheter in accord with previous studies.[6,7] Cardiac output was measured from the indicator-dilution curves sampled from the pulmonary artery after right atrial injection.[8,9] Three successive curves were used to calculate the forward flow. Stroke volume and stroke work were obtained as previously reported.[6]

Left ventricular ejection fraction was measured by indicator-dilution technique using cold saline solution rapidly injected into the left ventricle.[10] The thermistor for the ejection fraction was placed into the National Institutes of Health catheter, 1 to 2 cm above the aortic valve. Three or four such curves were obtained and end-diastolic volume was calculated as a ratio of mean stroke volume to mean ejection fraction.[11] Left ventricular ejection fraction obtained with this technique has shown good reproducibility in a model under nearly ideal conditions of mixing and sampling (mean coefficient of variation 3 percent).[11] Whereas the injection artifact appears to be negligible with the indicator-dilution method, angiographic dye can produce sustained depression of ventricular function, especially in the abnormal heart.[12] Despite a systematic difference between the two techniques, there is a good correlation of the ejection fraction that is derived from the indicator-dilution and angiographic techniques (correlation coefficient 0.824).[13]

The angiographic technique has yielded systematically lower values for end-diastolic volume than has the indicator-dilution method (averaging 13 percent lower in the study of Hugenholtz et al.[13] [correlation coefficient 0.96]). Although an absolute test of accuracy in vivo is not available, two additional studies[14,15] comparing the indicator-dilution technique with independent methods have shown good agreement. The latter study represents a revision of a previous conclusion that the indicator-dilution technique differs substantially from angiographic data.[16] For these reasons the indicator-dilution method was the primary technique used in this study. The dilution curves, pressures, left ventricular maximal dP/dt and electrocardiogram were recorded on an Electronics for Medicine DR-8 recorder.

Left ventricular function and contractility were estimated in several ways. Contractility was assessed in the intact animal from an index expressing the end-isometric force-velocity relation normalized for initial fiber length. This contractility index exhibits a relatively narrow range in normal ventricles, increases in a predictable fashion with positive inotropic interventions and is depressed in the presence of left ventricular disease.[17] The formulation includes $(dP/dt\ max/MIP)/2\pi r$, where dP/dt max is the maximal rate of rise and left ventricular pressures in mm Hg/s, MIP the maximal isovolumetric pressure in mm Hg, and $2\pi r$ the end-diastolic left ventricular circumference in cm.[17] The units of contractility are muscle length/s per cm of initial circumferential fiber length. The left ventricular radius was calculated from end-diastolic volume on the assumption that the ventricle was a sphere at the end of the isovolumetric period, and circumferential fiber length was calculated as $2\pi r$. Another index expressing the myocardial contractility used in this study was velocity of contractile element (V_{ce}) at peak dP/dt, calculated as the ratio of maximal dP/dt for simultaneous left ventricular pressure in accord with the method of Levine and Brittman.[18]

Left ventricular function was further assessed during volume expansion.[6] A second catheter was introduced into the left ventricle, and saline solution at the temperature of blood was infused at 48 ml/min for 3 to 5 minutes. During the saline infusion, end-diastolic pressure was continuously recorded at high sensitivity and the cardiac output and ejection fraction were determined immediately after 3 minutes of infusion when the animals were in a steady state as judged from heart rate, aortic pressure and ventricular end-diastolic pressure.

To determine if ventricular pressure increments during volume expansion are at least partially affected by enhanced intrapericardial pressure,[19] *three normal dogs were assessed in the intact anesthetized state.* A catheter was introduced into the pericardial space by a modification of the transseptal technique utilizing a small Odman-Ledin catheter and a Brockenbrough needle (infant size).[20] By this technique the catheter is advanced over the needle into the pericardial space after the latter penetrates the free wall of the right ventricle. To determine ventricular end-diastolic transmural pressures, catheter tips were located within the chest using the posteroanterior chest X-ray films taken at each stage of the study with correction made as necessary for magnification. Statham pressure transducers (P23Db) were placed at the level of the spine and circulatory and pericardial pressures were corrected to this reference level by subtraction or addition of 1 cm water for each centimeter of height; the respective catheter tip was above or below this level. Ventricular end-diastolic and pericardial pressures were recorded at high sensitivity (1 mm Hg equal to 4 mm paper) and were measured at end-expiration and by using averaged pressure levels throughout three respiratory cycles.

After infusion of normal saline solution at 50 ml/min into the left ventricular chamber for 4 minutes, intrapericardial end-diastolic pressure was -1 ± 0.6 mm Hg (mean ± standard

TABLE I

Left Ventricular Function at 18 Months in Three Groups of Dogs at Rest (mean ± standard error the mean)

	Group 1 (control)	Group 2 (smokers of low nicotine cigarettes)	Group 3 (nicotine users)	p Values		
				2 vs 1	3 vs 1	3 vs 2
Wt	11.6 ± 1.4	10.4 ± 0.7	9.1 ± 0.8	NS	NS	NS
HR	133 ± 13	153 ± 10	163 ± 23	NS	NS	NS
AoS	121 ± 4	114 ± 6	150 ± 14	NS	<0.05	<0.03
AoD	83 ± 5	81 ± 6	120 ± 14	NS	<0.02	<0.02
EDP	6.4 ± 0.8	5.6 ± 1.1	6.7 ± 1.7	NS	NS	NS
EDV	4.06 ± 0.61	3.80 ± 0.58	5.36 ± 0.94	NS	NS	NS
SV	1.30 ± 0.20	1.40 ± 0.2	1.18 ± 0.20	NS	NS	NS
EF	37 ± 2.8	38 ± 3.0	24 ± 3.3	NS	<0.04	<0.01
dP/dt	2455 ± 88	2211 ± 146	2071 ± 92	NS	<0.01	NS
V_{ce}	30.0 ± 2	28.0 ± 2.2	17.7 ± 1.3	NS	<0.002	<0.005
C_yI_x	2.18 ± 0.30	2.15 ± 0.18	1.28 ± 0.12	NS	<0.01	<0.005
TSR	4118 ± 364	3844 ± 161	7752 ± 1288	NS	<0.05	<0.009
SW	2.00 ± 0.28	2.06 ± 0.31	2.28 ± 0.39	NS	NS	NS

AoD, AoS = aortic diastolic and systolic pressures, respectively (mm Hg); Cylx = Frank-Levinson index of contractility (muscle lengths/s per cm); dP/dt = first derivative of left ventricular pressure (mm Hg/s); EDP = left ventricular end-diastolic pressure (mm Hg); EDV = left ventricular end-diastolic volume (ml/kg); EF = ejection fraction (percent); HR = heart rate (beats/min); NS = not significant; p = probability; SV = left ventricular stroke volume (ml/kg); SW = left ventricular stroke work (g-m/kg); TSR = total systemic resistance (dynes s cm^{-5}); V_{ce} = velocity of contractile element at peak dP/dt (muscle lengths/s); wt = body weight (kg).

error of the mean) compared with the control value of −2 ± 0.7 mm Hg, a nonsignificant change. Moreover, sampling of right heart blood before and after 4 minutes of saline infusion revealed no decrease in hematocrit or serum albumin, implying that much of the solution diffused out of the vascular system without recirculation in this time span. Thus, the filling pressure responses in the beagle during infusion of a proportionate amount of saline solution into the left ventricle are considered to be largely independent of intrapericardial pressure.

Electrophysiologic studies of left ventricular conduction were also performed, usually before the hemodynamic studies by an electrocatheter technique in accord with Ettinger et al.[21]

Myocardial histology: At the conclusion of these studies, the heart was rapidly arrested with iced Ringer' solution. Samples of the left ventricle, approximately 15 g, were taken from the periapical region for analysis of cation and myocardial lipids.[3] Sections were also taken from the left ventricular myocardium and left coronary artery for histochemical and microscopic studies by the pathologist without knowledge of identification.[3]

Because the myocardium of long-term smoking beagles has been found to accumulate collagen,[3] the presence of collagen was quantified by measuring the myocardial content of hydroxyproline.[22]

Statistical analyses: These were performed using conventional methods for small samples and variation reported as standard error. Differences between groups were evaluated with Student's unpaired *t* test. The *t* test for paired samples was used to evaluate the response to saline infusion within each group. Values are expressed as mean ± standard error of the mean.

Results

Nutritional state and blood chemical values: The dogs in group 1 (control group) and group 3 (nicotine users) behaved similarly to those reported on in our prior study.[3] In contrast to the control dogs, dogs in the two experimental groups did not gain weight during the observation period, but there was no statistical difference in weight among the three groups at the conclusion of the study. (Table I). The final indexes of nutritional state were comparable to initial values in the three groups. The final hematocrit levels were 39 ± 2, 38 ± 3 and 42 ± 1 percent, respectively, in groups 1, 2 and 3. Serum albumin levels were 3.8 ± 0.2, 3.6 ± 0.1 and 3.0 ± 0.8 g/100 ml in the respective groups. Serum potassium and sodium values (in mEq/liter) were 3.3 ± 0.3 and 3.2 ± 0.2, 4.8 ± 0.8 and 145 ± 1, and 140 ± 4 and 137 ± 6, respectively. No group exhibited changes in plasma levels of triglycerides, free fatty acids, phospholipids or cholesterol. The final values for serum triglycerides (mol/liter) and free fatty acids (μEq/liter) were 0.34 ± 0.08 and 0.34 ± 0.08, 0.35 ± 0.12 and 300 ± 35, and 292 ± 36 and 296 ± 40 in the three groups. Serum phospholipids and cholesterol values (mmol/liter) were 2.47 ± 0.31 and 2.54 ± 0.60, 1.86 ± 0.18 and 3.16 ± 0.31, and 3.59 ± 0.96 and 2.16 ± 0.96.

Carboxyhemoglobin: In group 2 (smokers) smoking three cigarettes, either of low nicotine content such as that in Sano or of high nicotine content as in a regular cigarette, over 30 minutes resulted in similar amounts of carboxyhemoglobin in the dogs in both the immediate and the late periods (Fig. 1). The carboxyhemoglobin values in g/100 ml after smoking three cigarettes of regular or low nicotine content were, respectively, 5.5 ± 1.0 and 4.9 ± 0.9 at 5 minutes, and 1.1 ± 0.1 and 1.8 ± 0.9 at 18 hours.

Hemodynamics and left ventricular contractility: The resting hemodynamic values in the three groups are shown in Table I. Compared with groups 1 and 2, the dogs receiving nicotine became hypertensive and had significantly higher values for systolic and diastolic pressures as well as peripheral resistance. There were no significant differences in pressure between groups 1 and 2. Heart rate, stroke volume, left ventricular end-diastolic volume, end-diastolic and pulmonary arterial pressures did not differ significantly among the three groups.

The ejection fraction in the dogs receiving nicotine (group 3) was reduced to 24 percent compared with 37 and 38 percent, respectively, in groups 1 and 2 (each p

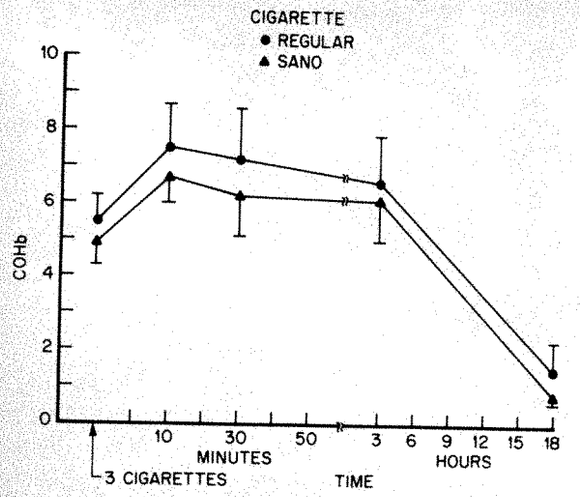


FIGURE 1. Carboxyhemoglobin (COHb) levels in dogs after smoking three cigarettes of regular or low (SANO) nicotine content in 30 minutes. These levels are similar in the two groups both during and 18 hours after smoking.

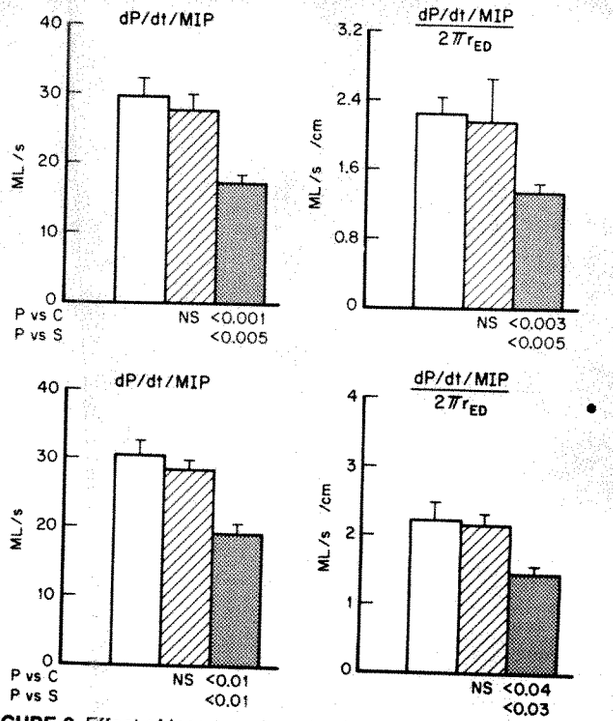


FIGURE 2. Effect of long-term low nicotine cigarette smoking (group 2 [S] **hatched bars**) and nicotine administration (group 3, **dotted bars**) on the indexes of left ventricular contractility and data in control dogs (group 1 [C] **open bars**) (**top**) and in three dogs from the two experimental groups with aortic pressure matching those in three control dogs (**bottom**). C = control group; dP/dt = rate of rise of left ventricular pressure; MIP = maximal isovolumic pressure (mm Hg); ML = muscle length; NS = not significant; P = probability; 2πrED = end-diastolic circumference (cm).

<0.001). Similar to the reduction in systolic performance characteristics, only the dogs receiving nicotine exhibited a deficit in the contractile function of the left ventricular muscle. This function was preserved in group 2, smoking low nicotine cigarettes. The contractility index in group 3 was 1.28 muscle length/s per cm compared with 2.18 in the control group and 2.15 in the smoking dogs ($p < 0.001$). The more readily measured index of contractility (namely, the velocity of contractile element of peak isometric stress (V_{ce}), which is not corrected for end-diastolic fiber length) also showed a similar reduction, 17.7 muscle lengths/s versus 30 and 28, respectively, in groups 1 and 2 ($p < 0.001$); no difference was noted between groups 1 and 2 (Fig. 2, top).

There was no correlation of the aortic pressure level and the indexes of left ventricular contractility. This was evidenced in three dogs from each group with similar levels of aortic diastolic pressure. The contractile deficit was still evident in the dogs receiving nicotine, even though the pressure was at approximately the same level as in the other two groups (Fig. 2, bottom). It thus appears that the contractile deficit is independent of increased afterload. To assess relative wall stiffness, saline solution was infused into the left ventricular chamber. A significantly higher end-diastolic pressure and tension was elicited in the dogs receiving nicotine, suggesting a decrease in left ventricular compliance; no such change was observed in either group 1 or 2 (Fig. 3).

Intracardiac conduction: To determine whether the reduced contractility may have been at least in part related to a delay in spread of excitation to the conduction fascicles and myocardium, His bundle electrograms were performed on the left side. All the intracardiac times in all dogs were essentially similar, indicating no gross delay of conduction through the myocardium of those receiving nicotine. The P-H times (ms) in groups 1 to 3 were, respectively, 71 ± 5, 66 ± 4 and 63 ± 5. The respective H-Q times (ms) were 27.6 ± 2.5, 26.8 ± 1.5, 30 ± 2.5; and the values for QRS duration (ms) were 57 ± 3, 60 ± 5 and 50 ± 5.

Myocardial pathology: At the conclusion of this study, the weight of the left ventricle and septum in g/kg of total body weight was 4.4 ± 0.4, 4.7 ± 0.4 and 5.4 ± 0.8 in groups 1, 2 and 3, respectively. On gross examination, the coronary arteries were normal, no visible intimal lesions were noted in any group.

The sole consistent morphologic abnormality on light microscopy consisted of collagen accumulation seen in the trichrome stain in group 3; there was no hypertrophy or inflammation. The presence of this collagen was confirmed by chemical analysis in the left ventricular wall. The hydroxyproline level was significantly increased in the left ventricular myocardium in the group receiving nicotine (6.61 ± 0.31 μg/mg dry weight versus 5.51 ± 0.11 and 5.8 ± 0.17 in groups 1 and 2, respectively) (Fig. 4). The myocardial composition of the lipid classes and major cations did not differ significantly in the three groups (Table II).

Discussion

Role of carbon monoxide: Carboxyhemoglobin levels similar to those found in heavy smokers have been reported to cause atherosclerotic changes and myocardial damage in animals.[23] Carbon monoxide is therefore considered a toxic component and has been postulated

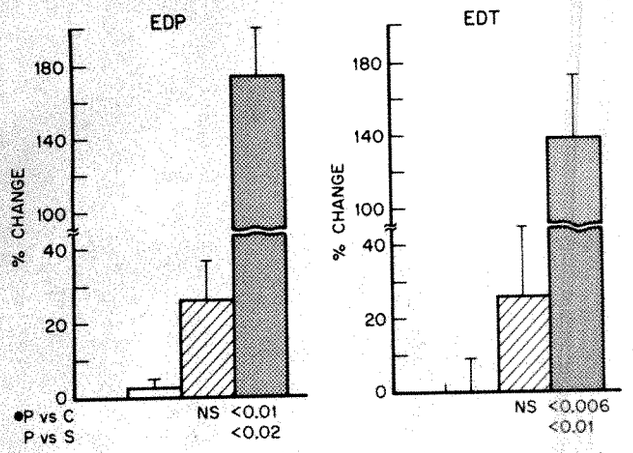


FIGURE 3. Changes (expressed as percent changes from preinfusion value) in end-diastolic pressure (EDP) and tension (EDT) after saline infusion, indicating a decrease in left ventricular compliance in animals receiving nicotine. **Open bars** = control dogs (group 1); **hatched bars** = low nicotine cigarette smokers (group 2); **dotted bars** = dogs receiving nicotine (group 3).

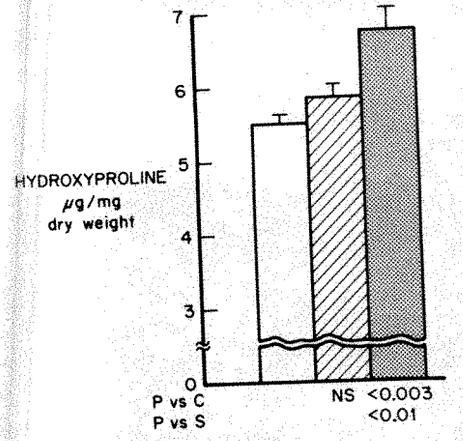


FIGURE 4. Collagen content of left ventricular myocardium expressed as hydroxyproline in three groups. Significantly increased levels are noted only in the dogs receiving nicotine (group 3). **Bars** as in Figures 2 and 3.

to have a major role in the cardiovascular disease due to long-term cigarette use.[4] An important basis for this current study is the observation that similar levels of carboxyhemoglobin result after smoking cigarettes with high, low or no nicotine content.[24] Because increases in systolic blood pressure and heart rate occur only after smoking nicotine-containing cigarettes, the acute hemodynamic responses appear to be independent of carbon monoxide.[25]

In this study we found that carboxyhemoglobin did not differ among beagles smoking three cigarettes of low or high nicotine content, either in the immediate postsmoking or late period (Fig. 1). In dogs smoking low nicotine cigarettes for 18 months there were no abnormalities of myocardial performance or composition.

Role of nicotine: In contrast, the group receiving nicotine exhibited a significant decrease in diastolic compliance during volume expansion compared with control animals. The decrease in left ventricular diastolic compliance appears to be related to the increased collagen content of the myocardium in the animals receiving nicotine. On the basis of separate studies of pericardial pressure during saline infusion, the pericardium was not considered to contribute to the decrease in ventricular distensibility, a finding supported by a recent study.[26]

The nicotine users were also characterized by a decrease in the contractility indexes in the basal state. Aortic pressure was elevated in this group and can reduce ventricular performance. However, there was no correlation between the level of aortic pressure in the dogs receiving nicotine and depression of indexes of left ventricular contractility. This was most evident in three dogs from each of the three groups, with similar levels of diastolic pressure (Fig. 2, bottom). Moreover, in a prior study aortic pressure was increased with angiotensin in the normal animal to the same levels as noted in animals receiving nicotine by infusion of angiotensin.[3] No reduction in the variables characterizing myocardial function was noted. Furthermore, in the early stages of chronic hypertension in man, ventricular performance is not uniformly diminished.[27] This would indicate that the reduction in ventricular performance by nicotine was not dependent on afterload. Ischemia does not appear to contribute to these abnormalities, because the coronary arteries were free of intimal disease and the myocardial cation content did not differ from that of control animals.

TABLE II

Myocardial Lipids and Cations at 18 Months in Three Groups of Dogs (mean ± standard error of the mean)

	Group 1 (control)	Group 2 (smokers of low nicotine cigarettes)	Group 3 (nicotine users)	p Values (2 vs 1, 3 vs 1, 3 vs 2)
LV wt	4.4 ± 0.4	4.7 ± 0.4	5.4 ± 0.8	NS
Trig	2.4 ± 0.8	2.3 ± 0.4	1.4 ± 0.8	NS
FFA	8.0 ± 0.6	6.7 ± 0.7	7.6 ± 0.6	NS
Phospho	24.8 ± 0.9	21.2 ± 1.9	21.1 ± 0.8	NS
Chol	5.31 ± 0.27	5.30 ± 0.14	4.55 ± 0.35	NS
Na	46 ± 4	44 ± 3	42 ± 4	NS
K	71 ± 2	66 ± 4	66 ± 5	NS
H_2O	79 ± 1	79 ± 1	80 ± 0.9	NS

Chol = cholesterol (μmol/g wet weight); FFA = free fatty acids (μEq/g); H_2O = water (percent); K = potassium (μEq/g wet weight); LV wt = weight of left ventricular septum (g/kg); Na = sodium (μEq/g wet weight); NS = not significant; p = probability; Phospho = phospholipids (μmol/g); Trig = triglycerides (μmol/g).

Myocardial changes: In this study, increases in collagen on chemical analysis were present only in the group receiving nicotine. This may be a result of increased synthetic activity of the fibroblasts in the interstitium as a result of long-term exposure to a sufficient quantity of nicotine. A limitation to velocity of contraction produced by associated changes in the elastic properties of myocardium may be responsible for the contractile deficit.[28] Although a direct effect of nicotine on the contractile mechanism by means of altered calcium mobilization has not been observed in short-term studies,[29] calcium fluxes have not been evaluated in long-term experiments.

Serum and myocardial lipids: Serum lipids were not changed in either the long-term smokers (group 2) or the group receiving nicotine, a finding that might have been altered by a high lipid diet. However, increments in serum cholesterol are reported to occur after administration of nicotine at higher dose levels than that of our study.[30] The normal myocardial lipid levels contrast with those of experimental alcoholism[6] and diabetes.[31] In these states, interstitial collagen accumulation is associated with enhanced triglyceride levels in cardiac cells. Altered myocardial composition after long-term cigarette use has previously been inferred from a morphologic study.

Implications: The cardiovascular responses of long-term nicotine administration in the beagle closely paralleled previous observations[3] in animals smoking regular cigarettes for many months but were in contrast to findings in the dogs in this study smoking low nicotine cigarettes. Thus it appears likely that the long-term effects of cigarette smoking on the myocardium are predominantly dependent on nicotine rather than on carbon monoxide.

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Electrophysiologic Effects of Imipramine and Doxepin on Normal and Depressed Cardiac Purkinje Fibers

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The tricyclic antidepressant drug imipramine may cause ventricular arrhythmias and intraventricular conduction disturbances in clinical use, particularly in patients who have ingested toxic doses or who have preexisting heart disease. Such effects have not been reported with doxepin, another tricyclic antidepressant drug. In this study, the electrophysiologic effects of these two drugs on normal and depressed canine Purkinje fibers were examined. Fiber depression was achieved by elevating potassium concentration [K^+] in the perfusate to 10 m*M*. In normal Purkinje fibers both imipramine and doxepin were tested in concentrations of 50, 250, 500 and 1,000 ng/ml. Both drugs had no effect on resting membrane potential but caused similar, dose-related reductions in action potential amplitude, maximal velocity of phase 0 depolarization ($\dot{V}_{max}$), action potential duration, conduction velocity and effective and functional refractory periods. Depressed fibers were exposed to only 250 ng/ml of imipramine and doxepin. Both drugs reduced conduction velocity and failed to alter the refractory periods of the depressed fibers whereas at the same concentration in normal fibers they caused no change in conduction velocity but shortened the refractory periods. The other electrophysiologic effects of the two drugs on depressed fibers were similar to those on normal fibers. These observations indicate that depressed fibers are more sensitive than normal fibers to certain electrophysiologic effects of both imipramine and doxepin, and that the different incidence rates of arrhythmias and conduction disturbances associated with the clinical use of these drugs is probably not due to differences in their direct electrophysiologic effects on the ventricular specialized conduction system.

Electrocardiographic abnormalities and cardiac rhythm disturbances are frequently observed in patients who have ingested toxic doses of tricyclic antidepressant drugs. Although intraventricular conduction disturbances occur most frequently, atrioventricular (A-V) block and ventricular tachyarrhythmias are also common.[1,2] There is evidence that even in therapeutic doses these drugs have significant effects on the electrophysiologic properties of the heart. Reversible T wave abnormalities are commonly observed in patients taking such doses of these agents,[1–4] and sporadic cases of reversible right and left bundle branch block and of complete heart block have been reported.[3,5–7] In a prospective study Vohra et al.[8] showed that prolongation of the H-V interval in the His bundle electrogram occurred in 5 of 12 patients given therapeutic doses of nortriptyline. Kantor et al.[7] carefully studied a patient who manifested 2:1 heart block while receiving a therapeutic dose of imipramine (Tofranil®) and showed that the heart block was directly related to the plasma concentration of the drug and occurred below the A-V node in the His-Purkinje system. These investigators[9] subsequently reported that therapeutic doses of imipramine administered to elderly depressed patients regularly caused prolongation of the P-R, QRS and Q-T intervals. It has been noted[10] that patients receiving therapeutic doses of amitriptyline have a greater than expected incidence of sudden death. Bigger et al.[11] reported on two depressed patients in whom

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therapeutic doses of imipramine significantly reduced the frequency of ventricular premature complexes.[11]

Among the various tricyclic antidepressant drugs, doxepin (Sinequan®) has been reported to cause no ventricular arrhythmias or conduction disturbances even when patients have ingested toxic doses or have heart disease.[8,12,13] With other tricyclic antidepressant drugs such as imipramine, such effects are rare in patients without heart disease when plasma levels of the drug are within the therapeutic range but they are virtually universal when plasma levels exceed 1,000 ng/ml.[13,14] It has been suggested that disturbances of intraventricular conduction, such as widening of the QRS complex, prolongation of the H-V interval and heart block, are more likely to occur at therapeutic blood levels of imipramine in patients who are elderly or who have preexisting heart disease, particularly disease of the ventricular specialized conduction system.[7,9]

This evidence indicates that among the tricyclic antidepressant drugs, some agents such as imipramine may cause cardiac arrhythmias, exert important effects on cardiac conduction (particularly in the His-Purkinje system) and manifest antiarrhythmic activity in patients with established ventricular arrhythmias, whereas other agents such as doxepin may not have these effects. This study was undertaken to determine if these differences could be explained on the basis of the direct electrophysiologic actions of these drugs on Purkinje fibers.

Methods

Experimental preparation: The hearts of healthy adult mongrel dogs weighing 10 to 20 kg were rapidly excised under general anesthesia with intravenous sodium pentobarbital (30 mg/kg body weight) and immediately dissected while immersed in cooled oxygenated modified Tyrode's solution containing (in mmol/liter): sodium chloride (137), sodium bicarbonate (12), dextrose (5.5), sodium phosphate (1.8), magnesium chloride (0.5), calcium chloride (2.8) and potassium chloride (4.0). False tendons were removed from the right and left ventricles, mounted in a tissue bath (volume 5 ml) and superfused at a flow rate of 20 ml/min with the Tyrode's solution equilibrated with 95 percent oxygen and 5 percent carbon dioxide at a temperature of 36 ± 1° C.

Stimulation and recording: All preparations were stimulated extracellularly at a cycle length of 800 ms with use of Teflon®-insulated bipolar silver electrodes located near one end of the preparation designated the proximal end. Basic drive stimuli were rectangular pulses 2 to 3 ms in duration and approximately twice diastolic threshold in amplitude. For experiments in which refractory periods were measured, premature impulses were delivered through the same electrode pair at selected intervals after the basic drive stimuli. The premature stimuli were rectangular pulses 2 to 3 ms in duration and greater than 5 times diastolic threshold. All stimuli were isolated from ground. Transmembrane potentials were recorded through glass microelectrodes filled with 3*M* potassium chloride and with tip resistances of 10 to 20 megohms. The microelectrodes were coupled by means of a silver-silver chloride electrode to a preamplifier with high input impedance (1.5×10^{12} ohms) and capacitance neutralization (constructed by S. Ross, Department of Pharmacology, Columbia University, New York, New York). The output of this preamplifier was displayed on a Tektronix model 5444 oscilloscope and photographed with a Grass model C4 oscilloscopic camera. The maximal rate of depolarization of action potentials was determined by electronic differentiation.[15]

Experimental protocols: Transmembrane resting and action potentials were initially recorded from all preparations after a minimum of 1 hour of perfusion with the modified Tyrode's solution described. Experiments were carried out only on preparations with Purkinje fibers exhibiting a resting membrane potential of −80 mV or more under these condi-

TABLE I

Effects of Imipramine (I) and Doxepin (D) on Resting and Action Potentials of Normal Purkinje Fibers

	Cells (n)	RMP (mV)	Amp (mV)	$\dot{V}_{max}$ (V/s)	APD_{50} (ms)	APD_{100} (ms)
Control	6	−83.5 ± 1.2	112.0 ± 2.3	592 ± 74	208 ± 15	358 ± 10
I, 50 ng/ml		−91.0 ± 3.7	114.0 ± 2.0	572 ± 49	211 ± 5	357 ± 9
Control	11	−84.1 ± 3.3	119.4 ± 3.0	449 ± 39	228 ± 13	371 ± 15
D, 50 ng/ml		−86.0 ± 2.9	122.4 ± 2.4	398 ± 39	210 ± 10*	366 ± 11
Control	14	−85.3 ± 11.8	118.7 ± 3.0	501 ± 64	223 ± 14	404 ± 19
I, 250 ng/ml		−88.7 ± 1.8	119.0 ± 3.1	414 ± 45	195 ± 10*	374 ± 5†
Control	29	−83.1 ± 1.3	118.6 ± 1.5	554 ± 27	216 ± 8	372 ± 6
D, 250 ng/ml		−84.3 ± 1.4	117.6 ± 1.6	499 ± 29†	178 ± 4†	346 ± 6†
Control	12	−84.9 ± 2.3	120.7 ± 3.1	481 ± 47	223 ± 12	379 ± 9
I, 500 ng/ml		−86.8 ± 1.6	121.0 ± 2.4	439 ± 42	179 ± 8†	356 ± 6†
Control	13	−82.8 ± 1.5	117.2 ± 2.1	381 ± 24	217 ± 11	416 ± 11
D, 500 ng/ml		−83.3 ± 0.8	114.9 ± 2.4	288 ± 33†	160 ± 5†	356 ± 5**
Control	21	−84.5 ± 1.7	118.9 ± 2.5	563 ± 47	237 ± 10	395 ± 14
I, 1000 ng/ml		−82.7 ± 1.3	114.6 ± 2.5*	451 ± 33†	154 ± 5†	350 ± 9†
Control	18	−79.5 ± 1.1	117.7 ± 1.8	512 ± 33	207 ± 9	365 ± 10
D, 1000 ng/ml		−81.4 ± 1.6	110.3 ± 2.6†	346 ± 32†	129 ± 3†	323 ± 5†

* $p < 0.05$; † $p < 0.01$ (statistical significance of the difference between control values and those obtained during drug exposure).
All values are expressed as mean ± standard error of the mean. The potassium concentration was 4.0 m*M* in all experiments. Amp = action potential amplitude; APD_{50} and APD_{100} = action potential duration at repolarization to 50 and 100 percent, respectively, of the amplitude of depolarization; RMP = resting membrane potential; $\dot{V}_{max}$ = maximal velocity of phase 0 depolarization.

tions. One of two different experimental protocols was then followed:

1. Normal tissues: Perfusion with Tyrode's solution was continued while two Purkinje fibers of the false tendon were impaled with microelectrodes, the proximal one lying within 1.5 mm of the stimulating electrode pair and the distal one lying 2 to 8 mm further toward the distal end of the preparation. The resting membrane potential, action potential amplitude, maximal upstroke velocity of phase 0 ($\dot{V}_{max}$) and action potential duration to repolarization to 50 percent and 100 percent of the amplitude (APD_{50} and APD_{100}, respectively) were recorded for each cell. The conduction time between the proximal and distal cells was determined by measuring the distance between mid point of the upstrokes of the two simultaneously displayed action potentials recorded at a rapid sweep speed. Then, with the transmembrane potentials of the two cells being recorded continuously on moving film, premature stimuli were introduced at progressively shorter coupling intervals after every eighth basic drive stimulus. The intervals between the responses to the basic drive and premature stimuli at the proximal site (P_1-P_2) and the distal site (D_1-D_2) were determined until excitation at the proximal site failed because of absolute refractoriness of those cells. The effective refractory period (ERP) was defined as the shortest P_1-P_2 interval at which conduction to the distal site was successful; the functional refractory period (FRP) was defined as the shortest D_1-D_2 interval achieved. After these recordings were made, imipramine or doxepin was added to the perfusate in a concentration of 50, 250, 500 or 1,000 ng/ml and observations were repeated after exposure to the drug for 40 minutes.

2. Depressed tissues: In these experiments depression of the Purkinje fiber action potentials was achieved by the addition of potassium chloride to the perfusing Tyrode's solution to give a final concentration of 10 mmol/liter. After 20 minutes of equilibration in this solution an experimental protocol identical to that outlined in (1) was followed except that the only concentration of imipramine and doxepin studied was 250 ng/ml.

Transmembrane resting and action potential data from an individual cell were not subjected to statistical analysis unless continuous impalement of the cell was maintained throughout the experimental protocol. If a microelectrode became dislodged in the course of an experiment it was replaced in the same or an adjacent cell by a small movement of the micromanipulator holding the electrode in the vertical plane only; the recordings obtained under such circumstances were used only for the determination of conduction times and refractory periods.

Analysis of data: Statistical analysis was performed using Student's *t* test for comparing means of nonindependent samples to assess the significance of any change caused by a given concentration of either drug in a given type of tissue preparation (normal or depressed). To compare the magnitude of change in an electrophysiologic variable caused in a given type of tissue preparation by the same concentration of the two different drugs, the *t* test for comparing means of independent samples was used.[16] In the latter case the change was first expressed as a percent of the control value for each experiment; the mean percent change was then determined for each of the two conditions being compared, and these two mean values were tested. A probability (p) value of <0.05 was considered significant.

Drugs: Pure drugs were obtained in powder form from their manufacturers: imipramine hydrochloride (Tofranil®, molecular weight 316.8) from Ciba-Geigy Canada Ltd., Dorval, Quebec, Canada and doxepin hydrochloride (Sinequan®, molecular weight 315.8) from Pfizer Canada Inc., Kirkland, Quebec, Canada. Fresh stock solutions were prepared each day by dissolving these drugs in double distilled water to give a final concentration of 100 mg/liter, and an appropriate amount of stock solution was then added to the Tyrode's reservoir to give the desired concentration. All doses of these drugs are expressed as concentrations of the salt.

Results

Effects on Normal Purkinje Fibers

Transmembrane resting and action potential characteristics (Table I): Neither imipramine nor doxepin exerted a measurable effect on the resting membrane potential of normal Purkinje fibers at concentrations of 50, 250, 500 or 1,000 ng/ml. However, marked effects were observed on the voltage time course of action potentials recorded from such fibers. The most sensitive variable was the action potential duration (APD), which was significantly shortened by both drugs in a dose-related manner. A significant effect (on APD_{50}) was apparent with doxepin at a concentration of 50 ng/ml; with imipramine, significant effects did not appear until a concentration of 250 ng/ml was tested. Shortening of APD_{50} was always more marked than that of APD_{100}, indicating that these drugs also caused a decrease in the slope of phase 3 of the action potential (Fig. 1).

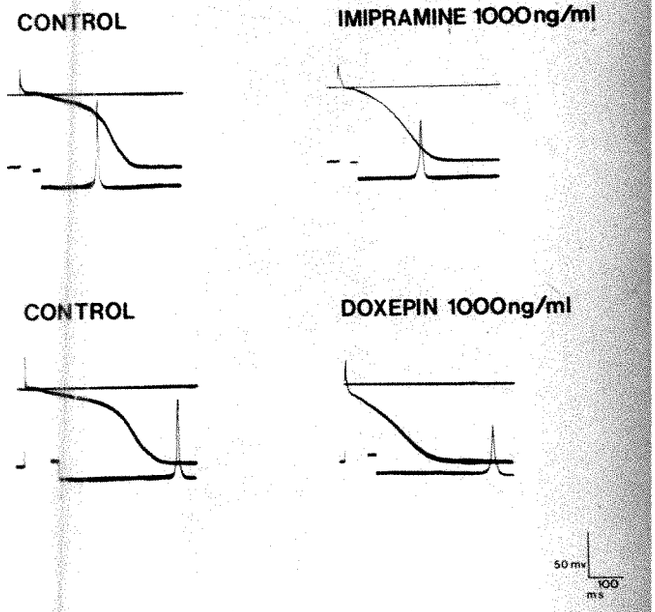


FIGURE 1. Effects of imipramine and doxepin on transmembrane resting and action potential characteristics of normal Purkinje fibers. In each panel the **upper tracing** is a zero reference potential, the **middle tracing** is a recording of the transmembrane potential, and the **lower tracing** is an electronic differentiation of the action potential upstroke preceded by a 200 V/s calibration square wave. The **left panels** were recorded under control conditions; the **right panels** were obtained after 40 minutes of exposure to imipramine, 1,000 ng/ml (**upper**) or doxepin, 1,000 ng/ml (**lower**). See text.

Both imipramine and doxepin also caused reductions in action potential amplitude and $\dot{V}_{max}$. With imipramine a significant effect on $\dot{V}_{max}$ was evident at a drug concentration of 250 ng/ml; with doxepin, this effect first achieved statistical significance at a concentration of 1000 ng/ml. A measurable effect on amplitude was apparent with both drugs only at a concentration of 1,000 ng/ml (Fig. 1).

Refractoriness and conduction (Table II): Both drugs reduced the effective and functional refractory periods of normal Purkinje fiber bundles (Fig. 2), an effect that was not surprising in view of the marked reduction of action potential duration. This effect was first apparent with each drug at a concentration of 250 ng/ml. The magnitude of the shortening of the functional refractory period was always very similar to that of the effective refractory period, indicating that the conduction velocity of early premature impulses was similar to that of the basic drive impulses. Conduction block of premature impulses between the proximal and distal recording electrodes was not observed. However, the conduction velocity of basic drive impulses was reduced by both imipramine and doxepin at concentrations of 1000 ng/ml, as indicated by the significant increases in conduction time that occurred (Fig. 2). The 47 percent increase that occurred with imipramine was not significantly different from the 25 percent increase with doxepin.

In fact, the effects of equivalent concentrations of imipramine and doxepin on the electrophysiologic properties of normal Purkinje fibers were generally quite similar. Although effects on certain variables such as APD_{50} and $\dot{V}_{max}$ achieved statistical significance when compared with control values at lower levels of doxepin than of imipramine (Table I), the mean percent changes produced by impramine were not significantly different from those caused by an equivalent concentration of doxepin for any measured variable at any drug concentration tested.

Effects on Depressed Purkinje Fibers (Tables III and IV):

Purkinje fibers that were depressed by increasing the concentration of potassium in the perfusate to 10 mmol/liter had low resting membrane potentials averaging about −63 mV. Action potentials recorded from such fibers had lower than normal values for $\dot{V}_{max}$, amplitude, APD_{50} and APD_{100} (Fig. 3). These were the expected effects of exposing Purkinje fibers to an increased extracellular potassium concentration.[17]

These depressed fibers were exposed only to a single concentration (250 ng/ml) of imipramine and doxepin. As in normal tissue, there was no detectable effect of either drug on resting membrane potential or action potential amplitude. Maximal upstroke velocity was reduced significantly only by imipramine; in normal tissues it had been reduced only by doxepin at this concentration. The APD_{50} and APD_{100} of the depressed fibers were further reduced by this concentration of imipramine and doxepin, as had been the case in normal fibers (Fig. 3). Despite these reductions, the effective and functional refractory periods of these depressed Purkinje fiber bundles were not shortened (Fig. 4). However, conduction time was increased significantly by both drugs at this concentration—a level that had not affected conduction time in normal preparations (Fig. 4).

Statistical comparison of the effects of imipramine with those of doxepin at this concentration on the electrophysiologic properties of depressed Purkinje fibers revealed no significant difference in any measured variables.

TABLE II

Effects of Imipramine (I) and Doxepin (D) on the Functional Properties of Normal Purkinje Fiber Preparations

	Preparations (n)	CT (ms)	ERP (ms)	FRP (ms)
Control	7	2.5 ± 0.5	276 ± 14	287 ± 12
I, 50 ng/ml		2.0 ± 0.5	276 ± 14	283 ± 11
Control	6	2.8 ± 0.4	307 ± 25	308 ± 24
D, 50 ng/ml		2.5 ± 0.4	288 ± 20	292 ± 19
Control	9	1.8 ± 0.2	296 ± 18	300 ± 17
I, 250 ng/ml		2.2 ± 0.2	278 ± 16	280 ± 15*
Control	6	2.2 ± 0.3	305 ± 13	307 ± 13
D, 250 ng/ml		2.1 ± 0.3	257 ± 10†	258 ± 10†
Control	6	1.8 ± 0.2	317 ± 26	317 ± 26
I, 500 ng/ml		2.0 ± 0.2	270 ± 21	270 ± 21
Control	13	2.3 ± 0.3	314 ± 15	314 ± 15
D, 500 ng/ml		2.6 ± 0.4	271 ± 15*	260 ± 5*
Control	13	1.8 ± 0.2	304 ± 26	307 ± 24
I, 1000 ng/ml		2.3 ± 0.2†	247 ± 34*	246 ± 11*
Control	15	1.9 ± 0.2	268 ± 14	269 ± 14
D, 1000 ng/ml		2.3 ± 0.3*	230 ± 12*	230 ± 12*

* $p < 0.05$; † $p < 0.01$ (statistical significance of the difference between control values and those obtained during drug exposure).
All values are expressed as mean ± standard error of the mean. The potassium concentration was 4.0 m*M* in all experiments. CT = conduction time from the proximal to the distal site; ERP = effective refractory period; FRP = functional refractory period.

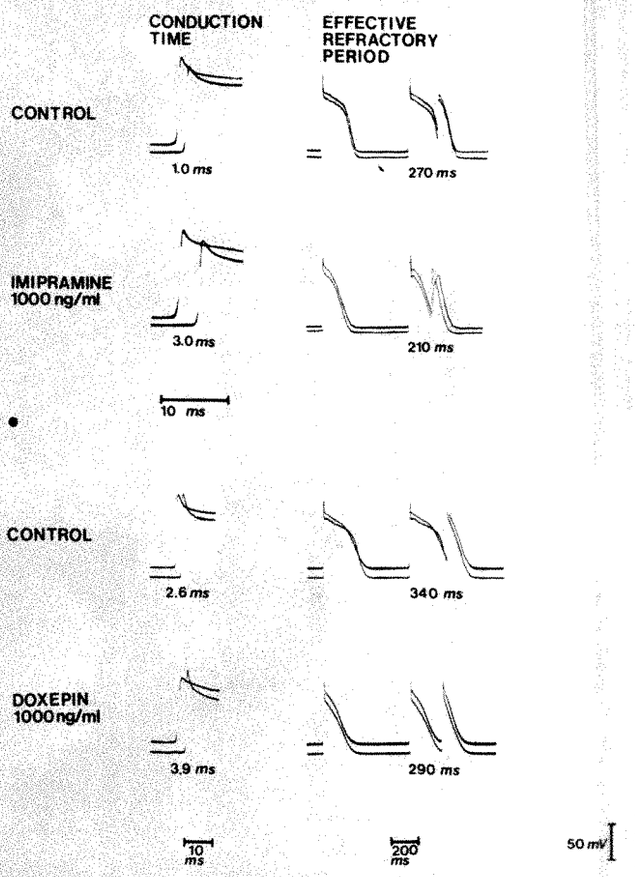


FIGURE 2. Effects of imipramine and doxepin on conduction and refractoriness in Purkinje fiber bundles perfused with Tyrode's solution having a potassium concentration of 4 mmol/liter. Each panel shows recordings made simultaneously from a proximal cell located within 2 mm of the stimulating electrodes and a distal one located approximately 4 mm farther along the bundle. The **left panels** illustrate the effects of these drugs on conduction time. Action potential upstrokes of the two cells are displayed at a rapid sweep speed. After 40 minutes of exposure to imipramine, 1,000 ng/ml, conduction time increased from 1.0 to 3.0 ms (**upper panels**). Exposure to an identical concentration of doxepin for the same period of time also resulted in an increase in conduction time, from 2.6 to 3.9 ms (**lower panels**). The **right panels** show the effects on the effective refractory period. Each panel shows the response of the two cells to the last two of a train of eight basic drive impulses at a cycle length of 800 ms, followed by the response to the earliest premature impulse that resulted in excitation at both the proximal and distal sites. Exposure to both imipramine and doxepin in concentrations of 1,000 ng/ml for 40 minutes resulted in marked shortening of the effective refractory period.

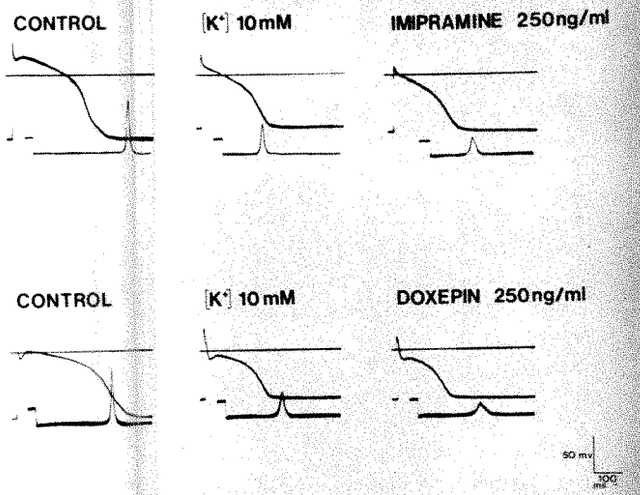


FIGURE 3. Effects of imipramine and doxepin on transmembrane resting and action potential characteristics of depressed Purkinje fibers. In each panel the **upper tracing** is a zero reference potential, the **middle tracing** is a recording of the transmembrane potential, and the **lower tracing** is an electronic differentiation of the action potential upstroke preceded by a 200 V/s calibration square wave. The **left panels** were recorded under control conditions with the fibers being perfused with normal Tyrode's solution. The **middle panels** were obtained after the fibers had been perfused for 20 minutes with Tyrode's solution containing a potassium concentration of 10 mmol/liter. The **right panels** were recorded 40 minutes after the addition of 250 ng/ml of imipramine (**upper**) or doxepin (**lower**) to the potassium-enriched Tyrode's solution. See text.

Discussion

An attempt was made to study concentrations of imipramine and doxepin that might occur in patients receiving these drugs. For imipramine the therapeutic range of plasma concentrations has been reported from as low as 95 to as high as 1,020 ng/ml[9,18]; for doxepin the range is from 19 to 250 ng/ml.[19–21] These figures represent total plasma concentrations not only of imipramine and doxepin but also of their active metabolites (desmethylimipramine and desmethyldoxepin, respectively). Imipramine has been estimated to be 75 to 95 percent protein-bound in vivo,[22] and hence the therapeutic range of the free drug would be correspondingly reduced. The extent of protein binding of

TABLE III

Effects of Imipramine (I) and Doxepin (D) on Resting and Action Potentials of Depressed Purkinje Fibers

	Cells (n)	RMP (mV)	Amp (mV)	V_{max} (V/s)	APD_{50} (ms)	APD_{100} (ms)
Control	20	−63.4 ± 1.2	84.6 ± 2.4	232 ± 29	141 ± 3	254 ± 5
I, 250 ng/ml		−64.4 ± 1.2	82.8 ± 2.2	152 ± 16†	133 ± 4†	243 ± 5*
Control	14	−62.6 ± 2.5	83.9 ± 2.7	226 ± 28	121 ± 10	231 ± 6
D, 250 ng/ml		−63.5 ± 2.1	80.5 ± 2.0	186 ± 27	105 ± 9†	209 ± 7†

* $p < 0.05$; † $p < 0.01$ (statistical significance of the difference between control values and those obtained during drug exposure).
All values are expressed as mean ± standard error of the mean. The potassium concentration was 10 m*M* in all experiments. Amp = action potential amplitude; APD_{50} and APD_{100} = action potential duration at repolarization to 50 and 100 percent, respectively, of the amplitude of depolarization; RMP = resting membrane potential; V_{max} = maximal velocity of phase 0 depolarization.

TABLE IV

Effects of Imipramine (I) and Doxepin (D) on the Functional Properties of Depressed Purkinje Fiber Preparations

	Preparations (n)	CT (ms)	ERP (ms)	FRP (ms)
Control	11	4.5 ± 0.8	220 ± 7	225 ± 7
I, 250 ng/ml		5.4 ± 0.9†	225 ± 8	230 ± 7
Control	9	4.3 ± 0.8	209 ± 7	218 ± 7
D, 250 ng/ml		6.2 ± 1.2*	201 ± 11	207 ± 12

* $p < 0.05$; † $p < 0.01$ (statistical significance of the difference between control values and those obtained during drug exposure).
All values are expressed as mean ± standard error of the mean. The potassium concentration was 10 m*M* in all experiments. CT = conduction time from the proximal to the distal site; ERP = effective refractory period; FRP = functional refractory period.

doxepin has not been reported. With these qualifications, and others to be discussed, it may be surmised that in our study the effects of imipramine or doxepin in a concentration of 250 ng/ml probably correspond with, or slightly exceed, the effects of a therapeutic plasma level in patients.

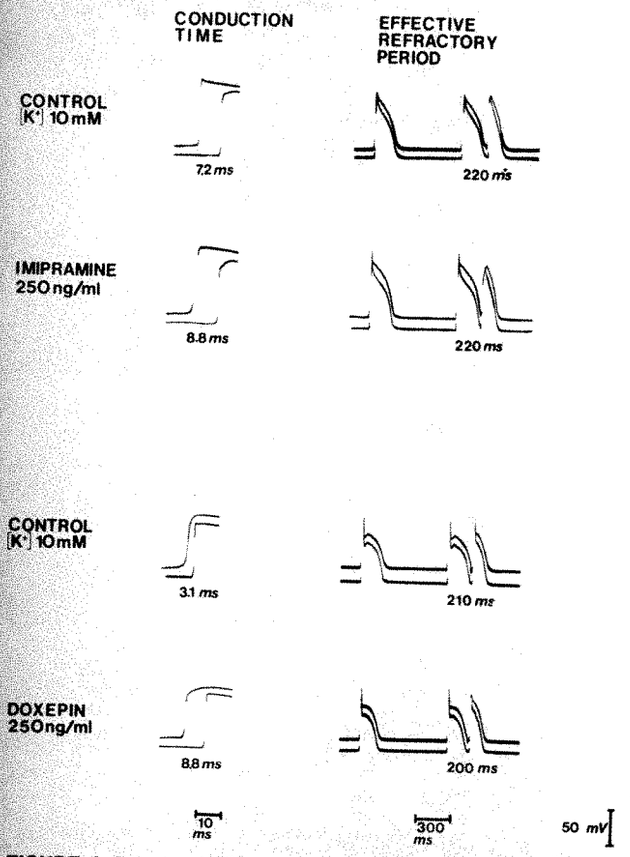


FIGURE 4. Effects of 250 ng/ml of imipramine (**upper panels**) and doxepin (**lower panels**) on conduction and refractoriness in depressed Purkinje fibers. Each panel shows simultaneous recordings from a proximal cell located within 2 mm of the stimulating electrodes and a distal one approximately 4 mm farther along the bundle. The potassium concentration in the perfusate was 10 mmol/liter in all recordings. In the **left panels** the action potential upstrokes are displayed at a rapid speed. Each **right panel** shows the response of the two cells to the last two of a train of eight basic drive impulses at a cycle length of 800 ms, followed by the response to the earliest premature impulse that resulted in excitation at both sites. The interval between these two impulses defines the effective refractory period. See text.

Comparative drug effects on normal Purkinje fibers: This study revealed that both drugs had similar effects on transmembrane resting and action potentials of normal Purkinje fibers. Neither imipramine nor doxepin affected resting membrane potential but each drug caused dose-related reductions of both action potential amplitude and $\dot{V}_{max}$, indicating a depressant effect on the rapid inward sodium current. Both drugs also shortened the action potential duration, an effect that cannot be explained on the basis of altered kinetics of the rapid inward sodium current and that implies either a reduction in slow inward current or an increase in outward current. The reduction of conduction velocity in normal Purkinje fibers observed at high drug concentrations could be due to the reductions of action potential amplitude and $\dot{V}_{max}$ because these are major determinants of conduction velocity,[23] whereas the drug-induced shortening of the effective and functional refractory periods could be explained by the reduction of action potential duration, because reactivation of the rapid inward sodium current is a highly voltage-dependent process.[24,25]

Comparative drug effects on depressed Purkinje fibers: The resting membrane potential was reduced to approximately −63 mV in some experiments by elevating the extracellular potassium concentration. This represented an attempt to alter the electrophysiologic properties of Purkinje fibers to simulate certain pathologic conditions, because reduction of the resting membrane potential is commonly observed in the cells of diseased hearts.[26–29] Such cells uniformly exhibit action potentials with reduced amplitudes and $\dot{V}_{max}$. Under the conditions used to depress Purkinje fibers in our study (potassium concentration 10 m*M*) the reduction in action potential amplitude and $\dot{V}_{max}$ was due to partial inactivation of the rapid inward sodium current.[24,25,30] The study did not examine the effects of imipramine and doxepin on severely depressed fibers exhibiting action potentials due entirely to the slow inward current.

On moderately depressed Purkinje fibers the effects of imipramine and doxepin were examined only at a concentration of 250 ng/ml in an effort to determine whether such fibers were more sensitive than normal fibers to therapeutic drug concentrations. With respect to transmembrane resting and action potential characteristics no such enhanced susceptibility was found. The effective and functional refractory periods of de-

pressed preparations, which were already considerably shorter than those of normal preparations (compare Table III with Table I), were unaffected by 250 ng/ml of imipramine and doxepin, that is, they were less influenced than those of normal tissues by this concentration of the drugs.

Comparative drug effects on conduction velocity: Perhaps the most important finding in this study was the effect of imipramine and doxepin on conduction velocity. Although both drugs slowed conduction in normal fibers only at a concentration of 1,000 ng/ml, a similar effect was apparent in depressed fibers at 250 ng/ml. In normal tissues this effect would be explained by reductions in action potential amplitude and $\dot{V}_{max}$ but in depressed tissues there was no clear relation between these variables and conduction velocity: $\dot{V}_{max}$ of depressed fibers was significantly reduced by 250 ng/ml of imipramine but not by doxepin, and action potential amplitude was not influenced by either drug. These findings imply that the drugs also affected one or more of the other determinants of conduction velocity such as membrane resistance, membrane capacitance or threshold for excitation.[23]

In previous studies[31,32] of the actions of imipramine on normal Purkinje fibers, it was found, as in this study, that the drug did not affect resting membrane potential but reduced $\dot{V}_{max}$ and action potential duration. In addition, Weld et al.[31] noted that imipramine increased the voltage threshold for excitation but did not affect the slope of spontaneous phase 4 depolarization. As in this study, Rawling and Fozzard[32] noted that imipramine caused slowing of conduction at a concentration of 1,000 ng/ml. They also found that it reduced membrane responsiveness, reduced the lowest transmembrane potential from which the cell could be stimulated and delayed the recovery of the rapid inward sodium current. Neither the effects of imipramine on depressed fibers nor the effects of doxepin on either normal or depressed fibers have previously been reported.

Clinical correlations: With respect to imipramine, the results of this study correlate with certain clinical observations. Slowing of conduction in normal Purkinje fibers at a high drug concentration (1,000 ng/ml) could explain the occurrence of intraventricular conduction disturbances and heart block in patients without heart disease who have ingested toxic doses of the drug. Ventricular tachyarrhythmias in such patients could be due to unidirectional block and reentry in the ventricular specialized conduction system as a result of drug-induced depression of conduction.[33] The observation in this study that depressed fibers are more sensitive than normal fibers to imipramine-induced slowing of conduction may explain the development of intraventricular conduction disturbances even with therapeutic doses of the drug in patients with heart disease. Finally, therapeutic doses of imipramine have been noted to decrease the frequency of ventricular premature complexes. Such complexes might be due to slow conduction, unidirectional block and reentry in the ventricular specialized conduction system.[33] Imipramine, by further depressing conduction in such regions, might abolish the unidirectional block and thereby abolish the premature complexes.[34]

In contrast, doxepin has not been reported to cause conduction disturbances or arrhythmias. This study suggests that this difference is probably not due to intrinsic differences between the direct electrophysiologic effects of doxepin and imipramine on the ventricular specialized conduction system but may be due to the generally lower plasma drug levels in patients receiving doxepin than in those receiving imipramine.

Other factors must also be considered. The assumption that the electrophysiologic effects of imipramine and doxepin on human and canine Purkinje fibers are similar in vivo and in vitro may or may not be valid. The metabolism of tricyclic antidepressant drugs in vivo produces metabolites that have antidepressant activity[35] and that may affect cardiac electrophysiologic properties; such effects were not assessed in this study. Finally, imipramine and doxepin produce adrenergic and anticholinergic effects[2,35] that probably influence the electrophysiologic properties of the heart. The present study did not examine the possible interactions of such indirect effects of these drugs with their direct electrophysiologic effects. Thus, although this study has shown that the direct electrophysiologic actions of imipramine and doxepin on isolated canine Purkinje fibers are similar, and that moderately depressed fibers are more sensitive than normal fibers to certain of these effects, further investigation is required before the clinical significance of these observations can be ascertained.

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In angina pectoris...

NITRO-BID®
(2% nitroglycerin)
Transdermal Ointment

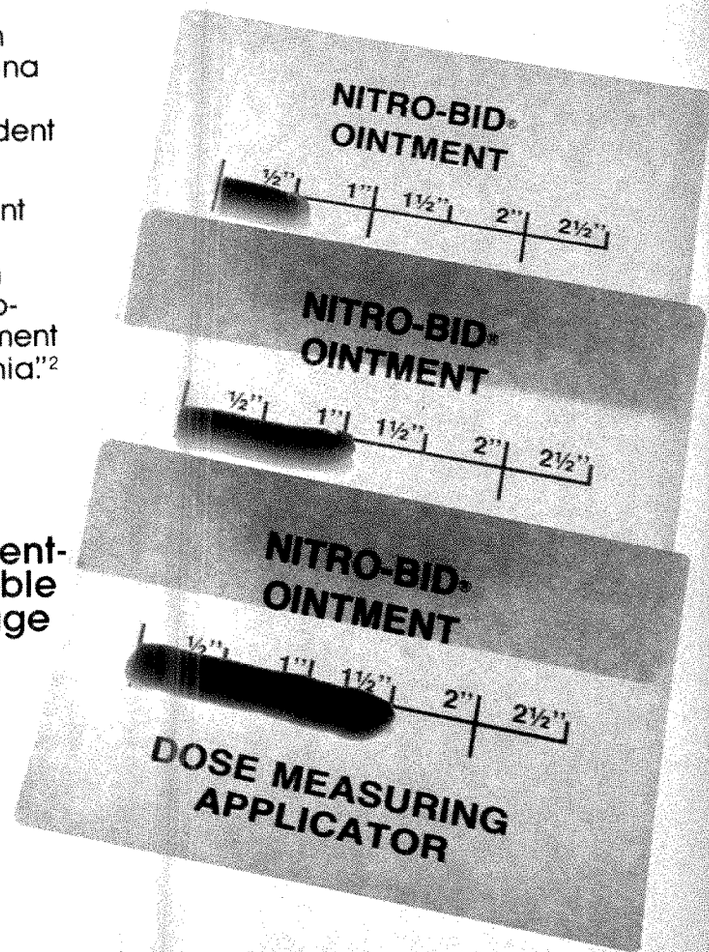
For prolonged prophylactic action

"Cutaneous administration of Nitroglycerin ointment (NITRO-BID®) in patients with angina pectoris exhibits prolonged action with evidence of pharmacological activity evident up to eight hours after application."[1]

"...data indicate that nitroglycerin ointment (NITRO-BID®) exerts profound reduction of peripheral arteriolar and venous tone with resultant alterations in left ventricular hemodynamic variables which afford enhancement of exercise tolerance and reduced ischemia."[2]



Patient-titratable dosage



Brief Summary:

Description: Nitroglycerin 2% (glyceryl trinitrate) and lactose in a special absorptive lanolin and white petrolatum base.

Action: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effects.

Indications: For the prevention and treatment of angina pectoris due to coronary artery disease.

Contraindications: In patients known to be intolerant of the organic nitrate drugs.

Warnings: In acute myocardial infarction or congestive heart failure, nitroglycerin ointment should be used under careful clinical and/or hemodynamic monitoring.

Precautions: Symptoms of hypotension, particularly when suddenly arising from the recumbent position, are signs of overdosage. When they occur, the dosage should be reduced.

Adverse Reactions: Transient headaches are the most common side effect, especially at higher dosages. Headaches should be treated with mild analgesics, and nitroglycerin ointment continued. Only with untreatable headaches should the dosage be reduced. Although uncommon, hypotension, an increase in heart rate, faintness, flushing, dizziness, and nausea may occur. These all are attributable to the pharmacologic effects of nitroglycerin on the cardiovascular system, but are symptoms of overdosage. When they occur and persist, the dosage should be reduced.

Dosage: Usual dose is 2 inches (50mm), as squeezed from the tube, every eight hours. Some patients may need 4 to 5 inches (100 to 125 mm) and/or application every four hours. Optimal dosage should be based upon clinical response, side effects, and effects of therapy upon blood pressure. Consult full product disclosure before prescribing.

References:

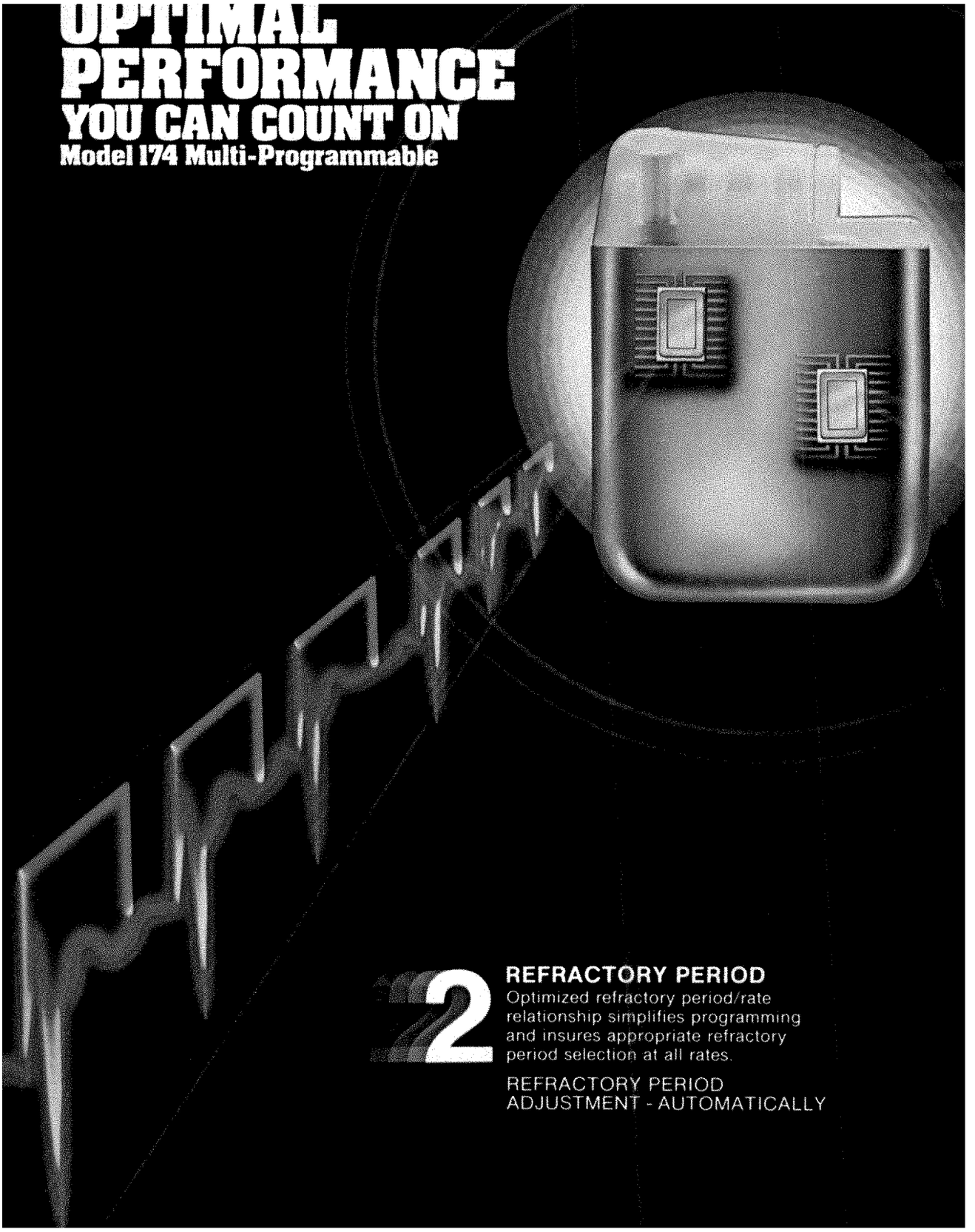
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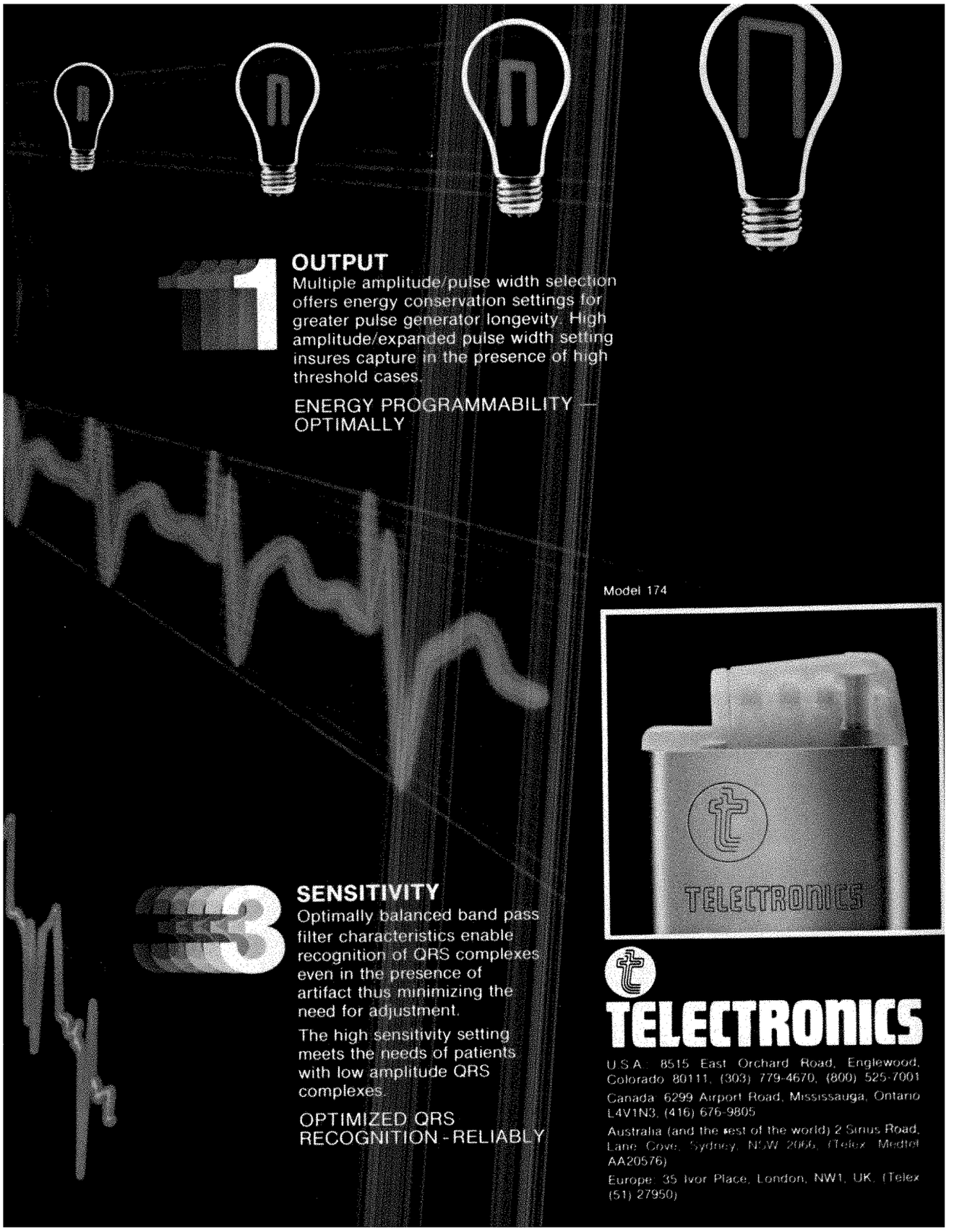
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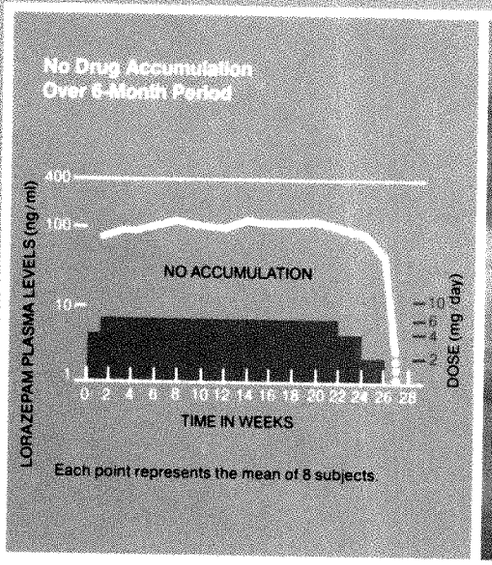
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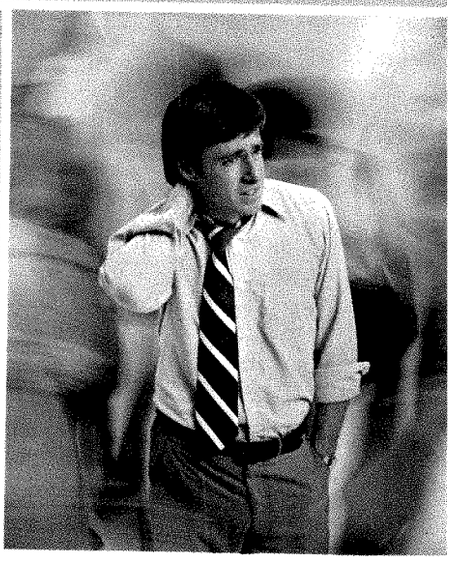
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How do you choose a minor tranquilizer?





Wyeth Laboratories
Philadelphia, PA 19101

Pharmacokinetics

Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

Consider the record of Ativan:



Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.



Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.



Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® (lorazepam) for Anxiety

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

NOTE: The CyberLith and the CyberLith Programmer are currently undergoing clinical evaluation.

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Our business is life.™

The CyberLith programming system.

Reliable, safe, convenient. And available.



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Convenient

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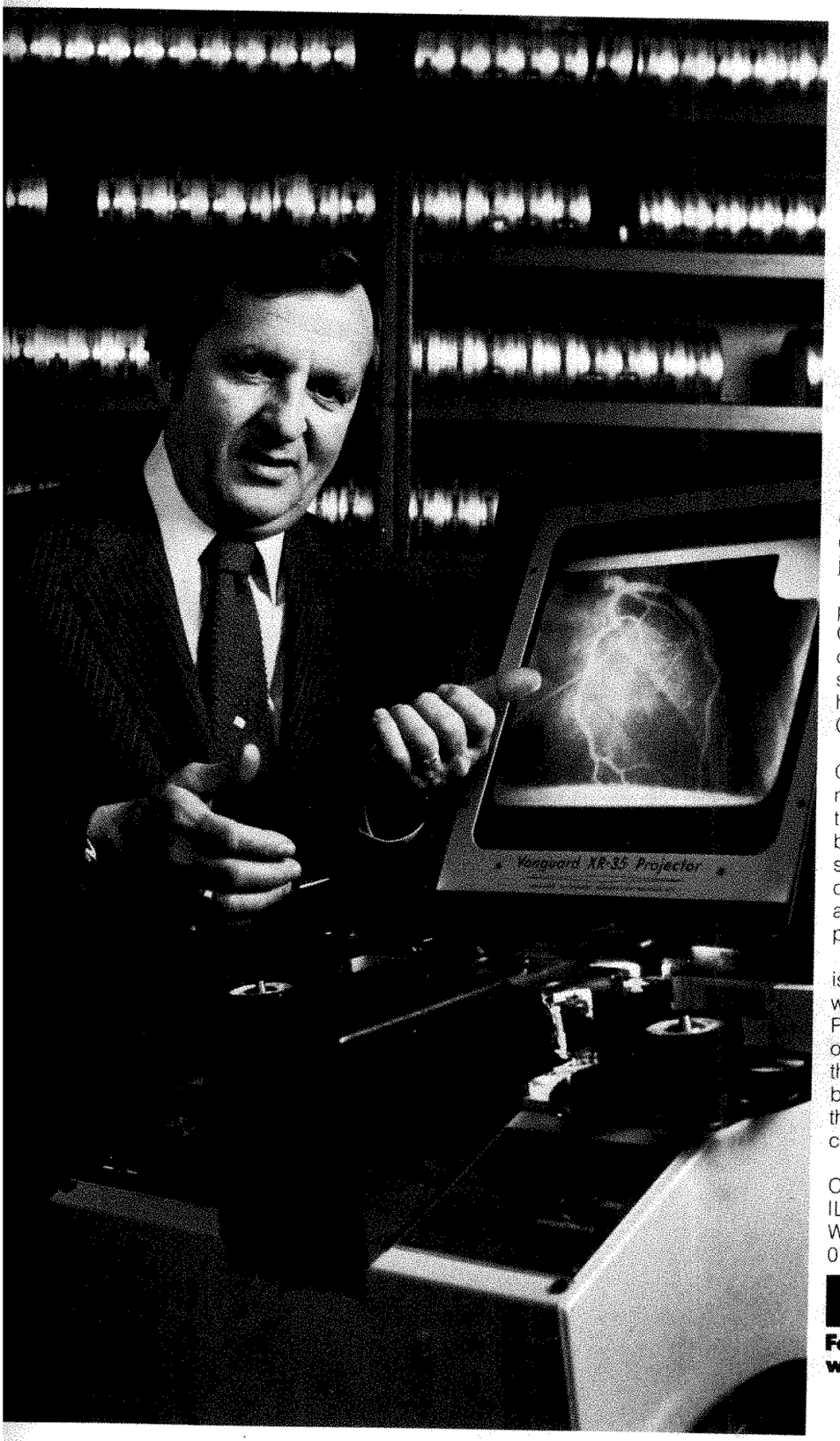
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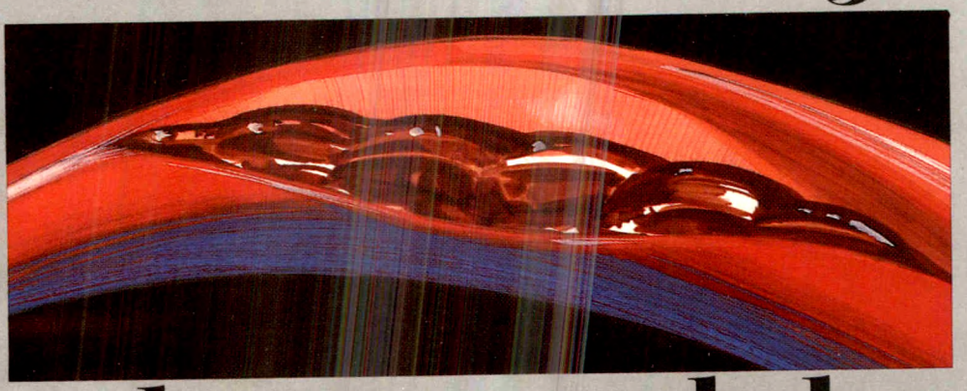
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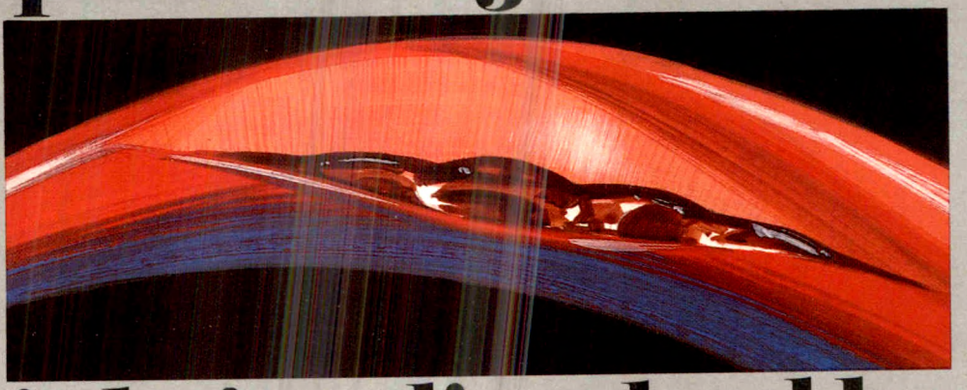
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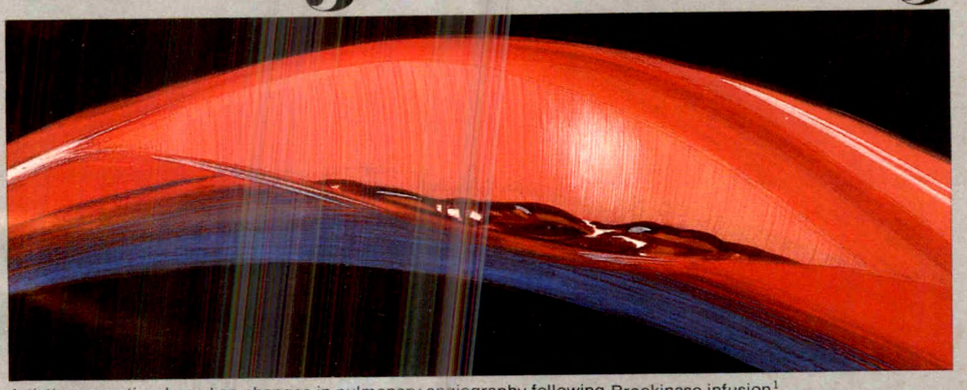
A life-threatening



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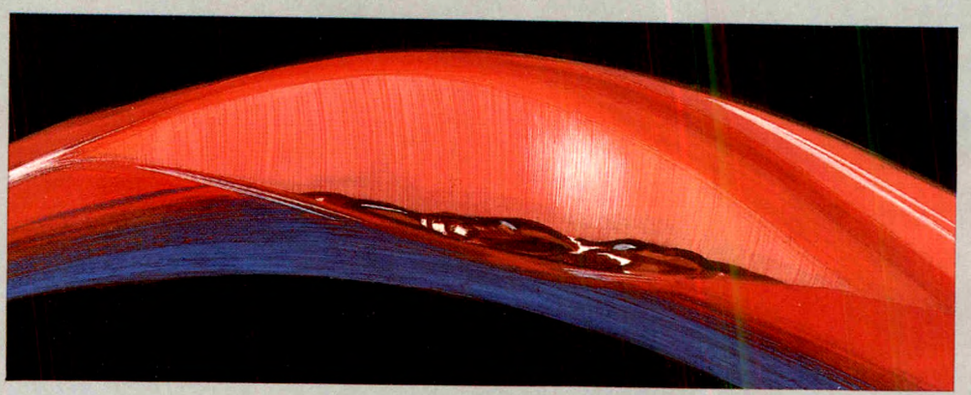
Artist's conception, based on changes in pulmonary angiography following Breokinase infusion.[1]

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Rapid and effective dissolution of pulmonary emboli.



- Proven by controlled clinical studies.[1]
- More rapid and effective than heparin alone during the first 24 hours after start of therapy.[2]

1. Sasahara AA, Hyers TM, Cole CM, et al: The urokinase pulmonary embolism trial. *Circulation* (Suppl II) 47:1-108, 1973.
2. Fratantoni JC, Ness P, Simon TL: Thrombolytic therapy: Current status. *N Eng J Med* 293:1073-1078, 1975.

Please see prescribing information on last page of this advertisement. It is important to pay close attention to WARNINGS and CONTRAINDICATIONS sections to minimize the risk of bleeding.

New Breokinase® is highly purified human protein.

- Lower incidence of fever.[3,4]*
- Can be used effectively in patients with recent streptococcal infections or high titers of streptococcal antibodies.
- Less risk of allergic reactions than streptokinase.†

Now urokinase therapy at lower cost

- Offers substantial savings to both hospital and patient.
- Convenient. Ask your Breon representative for a list of depots. There is one near you.

*Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established.

†In vitro and intradermal tests gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions occurring cannot be excluded. There have been rare reports of relatively mild allergic reactions such as bronchospasm and rash.

3. Sasahara AA, Bell WR, Simon TL, Stengle JM, Sherry S: The phase II urokinase-streptokinase pulmonary embolism trial. *Thrombos Diathes Haemorrh (Stuttg)* 33:464-476, 1975.

4. Urokinase pulmonary embolism trial study group: Urokinase-streptokinase embolism trial. *JAMA* 229:1606-1613, 1974.

Doctor: Before prescribing or administering Breokinase® (urokinase for injection) please read the following product information.

BREOKINASE®

(urokinase) for injection

Breokinase (urokinase for injection) should be used only by physicians with adequate experience in the management of thrombotic disease in hospitals where necessary clinical and laboratory monitoring can be performed (see Warnings, Precautions and Dosage and Administration).

The physician should carefully assess the overall clinical status and history of the patient before beginning urokinase treatment. Urokinase produces more profound changes in hemostasis and a greater frequency of bleeding than heparin or oral coumarin anticoagulant therapy. Bleeding when it occurs is more severe and more difficult to manage. Such factors as patient's age, physical condition, and underlying bleeding tendency (as described under Warnings and Precautions) should be taken into consideration when the potential risk of serious hemorrhage is weighed against the potential benefits of urokinase treatment.

Indications

Breokinase is indicated for the thrombolytic treatment of:

—acute massive pulmonary embolism, defined as obstruction or significant filling defects involving two or more lobar pulmonary arteries or an equivalent amount of emboli in other vessels, as seen on pulmonary arteriography;

—pulmonary embolism accompanied by unstable hemodynamics, i.e., inability to maintain blood pressure without supportive measures.

The diagnosis of pulmonary embolism should be confirmed by objective means, preferably pulmonary arteriography.

Urokinase treatment should be started as soon as possible after diagnosis of pulmonary embolism, but no later than five days after onset. Under these circumstances, angiographic and hemodynamic measurements and perfusion lung scans demonstrate a more rapid improvement during the first 24 hours after initiation of therapy than with heparin therapy. However, it has not been established that urokinase treatment decreases morbidity or mortality compared to heparin therapy alone.

Contraindications

Thrombolytic therapy increases the risk of bleeding. The risk of hemorrhage in the conditions listed below should be weighed carefully against the anticipated benefits of urokinase therapy in each patient. The benefits and risks associated with urokinase therapy should be compared to the benefits and risks associated with other forms of treatment.

1. Surgical procedures within preceding ten days (including liver or kidney biopsy, lumbar puncture, thoracenteals, paracentesis, extensive or multiple cutdowns).
2. Intraarterial diagnostic procedure within ten days.
3. Ulcerative wound.
4. Recent trauma with possibility of internal injuries.
5. Visceral or intracranial malignancy.
6. Pregnancy and the first ten days post-partum.
7. Actively bleeding lesion of the gastrointestinal or genitourinary tract, or a condition with significant potential for bleeding (including ulcerative colitis, diverticulitis).
8. Severe hypertension.
9. Acute or chronic hepatic or renal insufficiency.
0. Uncontrolled hypocoagulable state (including coagulation factor deficiency, thrombocytopenia, spontaneous fibrinolysis, any purpuric or hemorrhagic disorder).
1. Chronic pulmonary disease with cavitation, e.g., tuberculosis.
2. Subacute bacterial endocarditis or rheumatic valvular disease.
3. Recent cerebral embolism, thrombosis or hemorrhage (within at least two months) to avoid risk of bleeding into infarcted cerebral tissue.
4. Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to locate or control.

Warnings

Bleeding: Activation of the fibrinolytic system with urokinase causes a more profound change in the hemostatic status of the patient than does anticoagulant therapy with heparin or coumarin agents. The objective of urokinase therapy is the production of sufficient amounts of plasmin to lyse intravascular deposits of fibrin; however, fibrin deposits which provide hemostasis, for example at sites of needle punctures, will also undergo lysis, and bleeding from such sites may occur. The possibility of bruising or hematoma formation, especially with intramuscular injections, is substantial during thrombolytic therapy. Unnecessary clinical or diagnostic procedures should be avoided. It is important that close attention be paid to this section and the Contraindications section in order to minimize the risk of bleeding.

Intramuscular injections should be avoided during urokinase therapy, as with heparin therapy, because of the high risk of hematoma formation. Bleeding may occur at sites of recent invasive procedures. Therefore, arterial punctures must be avoided before as well as during treatment with urokinase. If arterial puncture is *absolutely* necessary, the radial or brachial artery should be used and the femoral artery must be avoided. Arterial puncture should be performed with great care by an experienced physician and pressure should be applied for at least 15 minutes. This should be followed by the application of a pressure dressing, and the puncture site should be checked frequently for evidence of bleeding.

Venipunctures should also be performed as carefully and infrequently as possible. If bleeding from an invasive site occurs during urokinase infusion, but is not severe, treatment may be continued with close clinical observation. Local pressure and other measures should be initiated immediately.

Spontaneous internal bleeding that is not accessible for the application of pressure may also occur. The risk of spontaneous bleeding is greater in patients with pre-existing hemostatic abnormalities, including patients whose histories are suggestive of prior bleeding problems whether or not there are demonstrable abnormalities in platelet count, prothrombin time, partial thromboplastin time, or bleeding time. The relative risks and benefits of urokinase treatment must be carefully assessed in such patients before initiating treatment.

Plasmin degrades fibrinogen, Factor V, Factor VIII, and other proteins in addition to fibrin. The products of plasmin degradation of fibrinogen and fibrin (FDP/fdp) possess an anticoagulant effect which may make bleeding difficult to control.

If serious spontaneous bleeding occurs, the infusion of urokinase should be terminated immediately, and treatment instituted as described under Adverse Reactions.

Risk of Cerebral Embolism

Urokinase treatment of patients with atrial fibrillation or other conditions which predispose to cerebral embolism may be hazardous because of the risk of bleeding into the infarcted cerebral area.

Use of Anticoagulants

Concurrent use of anticoagulants with urokinase may be hazardous and is not recommended. Before beginning urokinase infusion in patients being treated with heparin, the effects of heparin should be allowed to decrease, as evidenced by a thrombin time of less than twice normal or an activated partial thromboplastin time (APTT) of less than one and one-half times normal. Similarly, heparin should be withheld for four hours following urokinase therapy unless the prothrombin time is in the normal range.

Rethrombosis has been observed after completion of urokinase treatment. In order to minimize this risk, administration of intravenous heparin followed by oral anticoagulant therapy is considered a necessary adjunct following urokinase therapy (see Dosage and Administration).

Use in Pregnancy

See Contraindications.

Use in Children

Safety and effectiveness of urokinase therapy in children have not been established; therefore, treatment of such patients is not recommended.

Precautions

Drug Interactions

Drugs that may alter platelet function, e.g., aspirin, indomethacin, and phenylbutazone, should be avoided during urokinase treatment. The interaction of BREOKINASE with other drugs has not been studied.

Laboratory Monitoring

In patients who have received heparin, the thrombin time or APTT should be measured prior to starting urokinase. (See Warnings.) Similarly, the prothrombin time should be monitored during and following urokinase therapy prior to instituting heparin. (See Dosage and Administration.) During urokinase administration, the levels of fibrinogen, plasminogen, Factor V, and Factor VIII are usually substantially decreased, and the level of fibrin and fibrinogen degradation products (FDP/fdp) is increased. Reduced fibrinogen and increased FDP/fdp result in a prolongation of the prothrombin time. Changes in these tests serve as confirmation of the existence of a lytic state. There are no data to indicate that alteration of dosage is required on the basis of these tests, although as a general rule the prothrombin time should not be allowed to increase above 30 seconds.

Urokinase infusion should be terminated immediately if serious bleeding occurs.

Adverse Reactions

Careful observance of the contraindications, warnings, and precautions to the use of urokinase is essential to minimize the incidence and severity of adverse effects.

Bleeding

Incidence

In controlled clinical trials of streptokinase and urokinase, severe bleeding (requiring a transfusion of greater than two units of blood) was seen in 4% of streptokinase patients and 6% of patients receiving urokinase. Several fatalities due to cerebral hemorrhage have occurred during urokinase therapy.

Spontaneous bleeding of a less severe degree has been observed during urokinase treatment at about twice the frequency as that occurring during heparin therapy. Oozing of blood from sites of skin puncture is frequent; therefore, all invasive procedures, especially arterial punctures and intramuscular injections, should be avoided and intravenous punctures kept to a minimum before and during treatment with urokinase.

A moderate decrease in hematocrit not accompanied by clinically detectable bleeding was observed in about 20% of patients treated with urokinase.

Management of Severe Bleeding

Urokinase therapy must be discontinued if serious bleeding occurs. Packed red cells are indicated for large blood loss. Plasma volume expanders (other than Dextran) may be used to replace blood volume deficit. Whole blood may also be used if it alone is available. The use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for urokinase has not been documented, but its use may be considered if the hemorrhage is unresponsive to blood replacement (see Warnings).

Allergic Reactions:

Urokinase is a protein of human origin, and *in vitro* as well as intradermal tests in humans gave no evidence of induced antibody formation. However, the possibility of serious allergic reactions (including anaphylaxis) occurring during its use cannot be excluded. There have been rare reports of relatively mild allergic reactions, e.g., bronchospasm and skin rash.

Fever:

Febrile episodes occurred in about 2-3% of urokinase-treated patients. A causal relationship to urokinase has not been established. Symptomatic treatment with acetaminophen rather that aspirin is usually sufficient.

Dosage and Administration

Preparation

Reconstitute each vial of Breokinase by aseptically adding 8.0 ml of Sterile Water for Injection, U.S.P. (It is important that *only* Sterile Water for Injection, U.S.P., *without* preservatives, be used. Bacteriostatic Water for Injection or other diluents should not be used.) Swirl gently to avoid foaming. **Do Not Shake.** Because Breokinase contains no preservatives, it should not be reconstituted until immediately before using. Any unused portion of the reconstituted material should be discarded.

Each ml of reconstituted Breokinase contains 31,250 C.T.A. Units of urokinase activity.

Dosing

Breokinase is intended for Intravenous Infusion Only

Urokinase treatment should be begun as soon as possible after the occurrence of pulmonary embolism, and no later than five days after onset. A priming or loading dose of 2000 C.T.A. Units/lb (4400 C.T.A. Units/kg) of reconstituted Breokinase is given over a period of ten minutes. This is followed by a continuous infusion of 2000 C.T.A. Units/lb/hr (4400 C.T.A. Units/kg/hr) for 12 hours.

A constant infusion pump independent of all other intravenous systems should be used. Do not expose reconstituted solution to excessive heat, such as high intensity lights, during administration.

Anticoagulation Following Breokinase Treatment

At the end of Breokinase infusion, treatment with heparin by continuous intravenous infusion followed by oral anticoagulant therapy is recommended to minimize rethrombosis. Heparin treatment should begin 4 hours after Breokinase infusion, or sooner if the prothrombin time has returned to normal. See manufacturer's prescribing information for proper use of heparin.

How Supplied

Breokinase is supplied as a sterile lyophilized preparation. Each vial contains 250,000 C.T.A. Units of urokinase activity and approximately 0.9 millimols sodium phosphates. The vials should be stored at or below 4° C.

BREON Breon Laboratories Inc.
90 Park Avenue
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Transcutaneous Method of Measuring Doppler Cardiac Output—I

Comparison of Transcutaneous and Juxta-aortic Doppler Velocity Signals With Catheter and Cuff Electromagnetic Flowmeter Measurements in Closed and Open Chest Dogs

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Cardiac output values obtained by thermodilution technique in 20 closed and open chest dogs were compared with values obtained by multiplying the integral of Doppler systolic velocity signals of aortic flow in 1 minute by the cross-sectional area of the aortic root. Doppler velocity signals were measured either from immediately outside the proximal aortic wall or from outside the chest wall during (1) the baseline state, (2) after 500 ml of hemorrhage, and (3) after reinfusion, (4) after administration of propranolol, and (5) during infusion of dopamine. In addition, Doppler "stroke volume" waveforms were compared with those obtained by electromagnetic flowmeter. Results showed a close similarity between Doppler signals and electromagnetic waveforms, and a close correlation between Doppler and thermodilution values for cardiac output except at heart rates exceeding 160 beats/min. The studies showed the transcutaneous Doppler method of measuring cardiac output to be an accurate and reliable technique with application to clinical heart disease.

The noninvasive measurement of cardiac output has been of interest to clinicians for years. Echocardiography is a useful technique but is not accurate in patients with large ventricular volumes or dyskinetic myocardial segments. Furthermore, an adequate left ventricular view is not obtainable in many patients. Radionuclide gated blood pool scanning appears to be an excellent noninvasive method for measuring cardiac output, ejection fraction and other indexes of ventricular performance. However, the expense of equipment and the safety procedures necessary for the preparation of isotopes may limit its availability in some hospitals. Aortic systolic velocity measurements have been obtained using a transcutaneous continuous wave Doppler velocity meter in human beings[1] and in laboratory animals.[2] Changes in the analog integral of the systolic velocity curve have shown a close correlation with changes in stroke volume extrapolated from cardiac output values obtained by thermodilution. To determine whether the velocity signals obtained with a remotely positioned transcutaneous Doppler probe were similar to those obtained with a Doppler probe positioned 1 cm from the aorta and with those from an electromagnetic flow probe, we performed the following study in closed and open chest dogs under controlled conditions as a prelude to studies in human beings.

Methods

Experimental protocol: Twenty mongrel dogs of either sex weighing from 18 to 30 kg were anesthetized with thiamylal sodium (30 mg/kg body weight) and morphine sulfate (3 mg/kg) subcutaneously, intubated and mechanically ventilated. A heparin-filled catheter was placed in the left ventricle retrograde from the right femoral artery. An electromagnetic catheter flow probe (Carolina Medical Electronics model EP 1008P) was positioned in the proximal aorta and energized with an electromagnetic flowmeter (Carolina Medical Electronics). A balloon-tipped flotation catheter (Edwards Laboratories) was positioned in the pulmonary artery and thermodilution cardiac output was measured with an Edwards cardiac output computer (model 9510-A).

From the Department of Medicine (Cardiology), Emory University School of Medicine, Atlanta, Georgia. This study was supported in part by a Grant-in-Aid from the American Heart Association (Georgia Chapter), Atlanta, Georgia. Manuscript received October 2, 1979; revised manuscript received April 21, 1980, accepted April 29, 1980.

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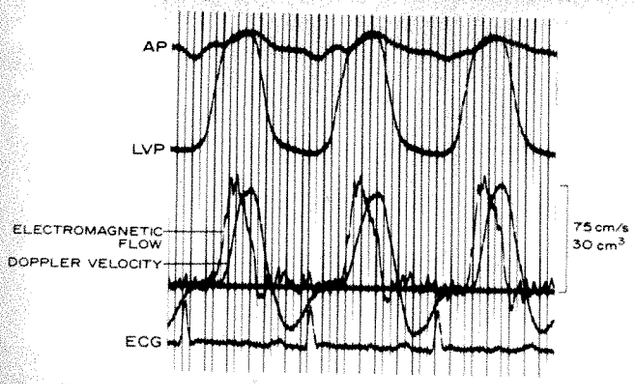


FIGURE 1. Representative tracing showing simultaneous electromagnetic flow and Doppler velocity signals. The Doppler probe is outside the thoracic cage. The 75 cm/s calibration applies to the peak velocity. The 30 cm^3 refers to the actual stroke volume of the electromagnetic flow signal depicted. Time lines are 0.04 second apart. AP = arterial pressure; ECG = electrocardiogram; LVP = left ventricular pressure.

Closed chest measurements: The transducer (diameter 16.0 mm) of a 2.2 megahertz bidirectional continuous wave Doppler velocity meter (Bach-Simpson Limited, model BVM20) was positioned superior to the right clavicle approximately 2 cm lateral to the suprasternal notch. The probe direction resulting in the maximal peak velocity from the proximal aorta was fixed with a C clamp attached to an overhead bar. All signals were recorded on an Electronics for Medicine eight channel recorder. Signals from the Doppler velocity meter and the electromagnetic catheter flow probe were recorded simultaneously while thermodilution cardiac output values were obtained. Measurements were made (1) in the baseline state, (2) after 500 ml of blood was removed through an arterial catheter, (3) after reinfusion of the blood in 100 ml increments, (4) during an infusion of dopamine in doses of 4, 10 and 16 μg/kg per min, and (5) after intravenous administration of propranolol (0.5 mg/kg).

Open chest measurements: After all closed chest measurements were completed, the chest was opened and an electromagnetic cuff flow probe (Carolina Medical Electronics, model EMP-445 or EMP-450) was placed snugly around the proximal aorta. The transducer (diameter 11 mm) of an 8 megahertz continuous wave Doppler ultrasonic velocity meter (Sonicaid Limited, model BV 381) was positioned just above the cuff flow probe and separated from the aortic wall by a thin membranous bag of ultrasonic gel (approximately 5 ml capacity) to dampen artifacts produced by aortic wall motion. The direction of the internal Doppler probe was varied to obtain the maximal peak velocity and was consistently parallel to the caudocephalad direction of the proximal aorta. The external transcutaneous Doppler probe was repositioned as previously described; however, the main pulmonary artery and brachiocephalic vessels were each temporarily occluded by clamping to determine whether aortic flow velocity alone was being measured. The two Doppler signals, the electromagnetic flow probe signal and thermodilution cardiac output values were recorded under the various hemodynamic conditions produced with the chest closed.

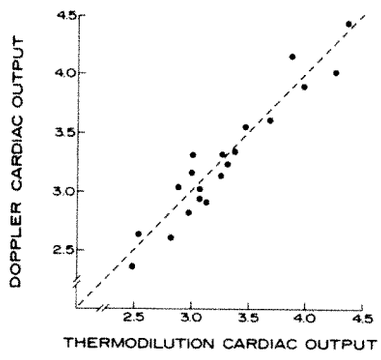


FIGURE 2. Linear regression plot of Doppler against thermodilution cardiac output values in liters/min for each of the 20 dogs during the baseline state. The **dashed line** is the line of identity. The correlation coefficient for the regression line is 0.96, slope = 0.98, the y intercept = 0.12, and the standard error of the estimate is 0.06 liters/min.

Standardization of signals: *Doppler signals:* Both Doppler instruments are provided with a square wave stimulus with a magnitude of either 50 or 100 cm/s for standardizing the measured instantaneous and peak velocities. Zero flow was obtained in the open chest dogs by temporary occlusion of the aorta, and electronically in closed chest dogs.

Electromagnetic flowmeter signals: Both the electromagnetic catheter flow probe and the cuff flow probe signals were calibrated by dividing the values for cardiac output obtained by thermodilution by the pulse rate. The cuff flow probe was also calibrated by cutting out the segment of aorta containing the probe and measuring mean flow of heparinized blood produced by a source with a known flow rate.

Analog integrator: The area beneath each Doppler velocity signal was automatically determined using a two channel in-line analog integrator (Carolina Medical Electronics, model 312).

Doppler signal processing: The continuous wave Doppler-shift frequencies were processed with a zero-crossing detector. This detector converts the frequency information to an analog voltage output that represents the root-mean-square of velocity of blood in the vessel in the region of the insonating Doppler beam.

Calculation of stroke volume from Doppler signals: The circumference of the aorta at the attachment site of the cuff flow probe was measured and the cross-sectional area (A) was calculated from the circumference (C) using the formula $A = C^2/4\pi$. A cardiac output value was calculated by multiplying the aortic cross-sectional area by the sum of the velocity integrals in systole for a 1 minute period (area × length [or distance of flow] = volume). Stroke volume was calculated by multiplying the aortic cross-sectional area by the height of an individual velocity integral.

Statistical methods: The following comparisons of values for stroke volume were made using linear regression[3]: (1) transcutaneous Doppler with catheter flow probe (closed chest dogs); (2) juxta-aortic Doppler with cuff flow probe; (3) transcutaneous with juxta-aortic Doppler; and (4) transcutaneous Doppler with cuff flow probe (open chest dogs). A correlation coefficient, slope, y intercept, and standard error of the estimate were calculated using values obtained in each dog separately because a regression analysis using values obtained in all dogs under different conditions is not statistically valid. We did, however, construct a regression line for values obtained in all dogs during the baseline state only.

Results

Experiments in Closed Chest Dogs

Comparison of waveforms: The Doppler waveform remained positive throughout systole, peaked between one third and one half of its total duration and usually had a brief negative dip in early diastole followed by a small positive wave in late diastole. The transcutaneous

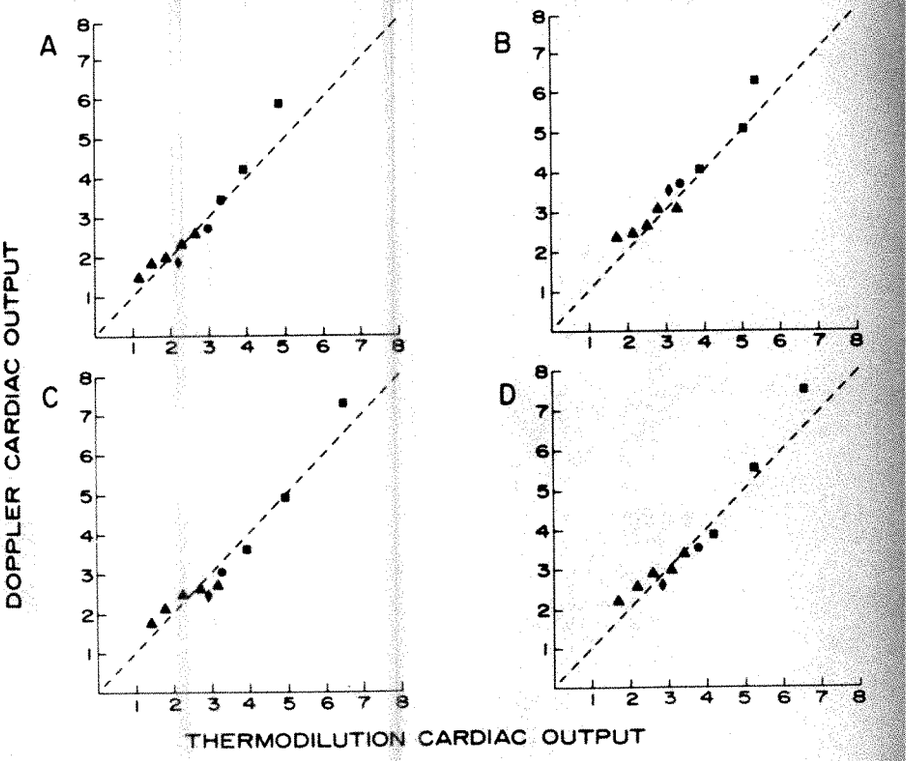


FIGURE 3. The values for cardiac output measurements (in liters/min) obtained by the Doppler method plotted against simultaneous thermodilution values for four representative dogs under the various hemodynamic conditions of the protocol. For dog A, the correlation coefficient (r) = 0.97, slope = 1.16, y intercept = 0.29; for dog B, r = 0.97, slope = 1.01, y intercept = 0.23; for dog C, r = 0.96, slope = 1.04, y intercept = −0.10; and for dog D, r = 0.96, slope = 1.07, and the y intercept = −0.09. **triangles** = hemorrhage; **diamonds** = propranolol; **circles** = baseline; **squares** = dopamine infusion.

Doppler velocity waveform and that produced by the electromagnetic catheter flow probe were generally similar in shape and magnitude in the baseline state, after 500 ml hemorrhage and at various stages during reinfusion, during the administration of dopamine at each of the three infusion rates and after administration of propranolol. However, the onset, duration and point of zero flow were slightly different with the two techniques, probably because, unlike the electromagnetic flow waveform, the Doppler signal represents the root-mean-square value for velocity (Fig. 1). This was exaggerated during dopamine infusion and after a premature ventricular beat. The reason for this exaggeration is unclear, but may be due to turbulence produced with more rapid ejection during dopamine infusion and after a premature beat, which would broaden the spectrum of frequencies detected by the Doppler instrument.

Comparison of cardiac output values: Cardiac output values ranged from 1.2 liters/min after 500 ml hemorrhage to 7.6 liters/min during maximal dopamine infusion. Figure 2 shows the correlation between values calculated from the Doppler velocity integrals and from the thermodilution method in all 20 dogs in the baseline state. In Figure 3, the values from four representative dogs are shown under various hemodynamic conditions. The average correlation coefficient of the regression lines for all 20 dogs was 0.92 (range 0.86 to 0.98). The values obtained after 500 ml hemorrhage and during the 16 μg/kg per min infusion of dopamine are farther from the line of identity than are those measured during the baseline state, during reinfusion of blood or after administration of propranolol. This proved to be a function of heart rate, as shown in Figure 4, in which the differences between the Doppler and thermodilution values are plotted against the heart rate; the most rapid rates occurred after 500 ml hemorrhage and during the 16 μg/kg per min infusion of dopamine. Results from other studies[4] have indicated that this inaccuracy of the Doppler method is probably a result of turbulent flow.

Experiments in Open Chest Dogs

Comparison of juxta-aortic Doppler and cuff electromagnetic flow probe signals: The velocity signal of the Doppler instrument and the signal produced by the electromagnetic cuff flow probe were similar in shape and magnitude, except that the peak of each Doppler signal occurred approximately 0.08 second after the peak "flow" signal.

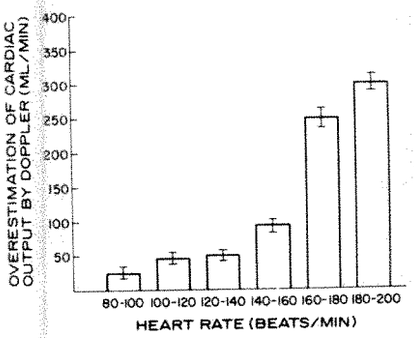


FIGURE 4. The differences (in ml/min) between Doppler and thermodilution values for cardiac output are shown for all 20 dogs at various ranges of heart rate. At higher heart rates the Doppler values overestimated thermodilution values more than at lower heart rates. Values are mean ± standard error.



FIGURE 5. Simultaneous signals produced by transcutaneous and juxta-aortic Doppler probes with the same amplification and identical 75 cm/s calibrations. ECG = electrocardiogram.

Comparison of transcutaneous and juxta-aortic Doppler signals: The velocity signals recorded transcutaneously and from within 1 cm of the wall of the aorta were nearly identical except for a lower signal to noise ratio in the transcutaneous signal, a result of the distance between the probe and the aorta and the movement of the chest wall and lungs in the artificially ventilated dogs (Fig. 5). This similarity held true under all hemodynamic conditions and at all heart rates encountered.

Simultaneous transcutaneous Doppler, juxta-aortic Doppler and cuff flow probe: When the three methods of estimating stroke volume were performed simultaneously, it was possible to determine the factors related to the greatest variance between Doppler estimations of stroke volume (by either method) and cuff flow probe measurements. Figure 6 shows stroke volumes calculated from both Doppler signals plotted against the stroke volumes measured by cuff flow probe. At very low and very high stroke volumes, both Doppler methods tended to overestimate the cuff flow probe value; however, the standard error of the estimate was still small (less than 4.3 ml) so that a high degree of accuracy was present throughout the range of stroke volumes. The percent of measured stroke volume estimated by both Doppler methods was found to be inversely proportional to the preceding R-R interval (Fig. 7), an observation that is consistent with the errors noted after an extrasystolic beat and at rapid heart rates. Thus, rapid heart rates and not absolute stroke volume appear to be major limitation of the method in the anesthetized dog.

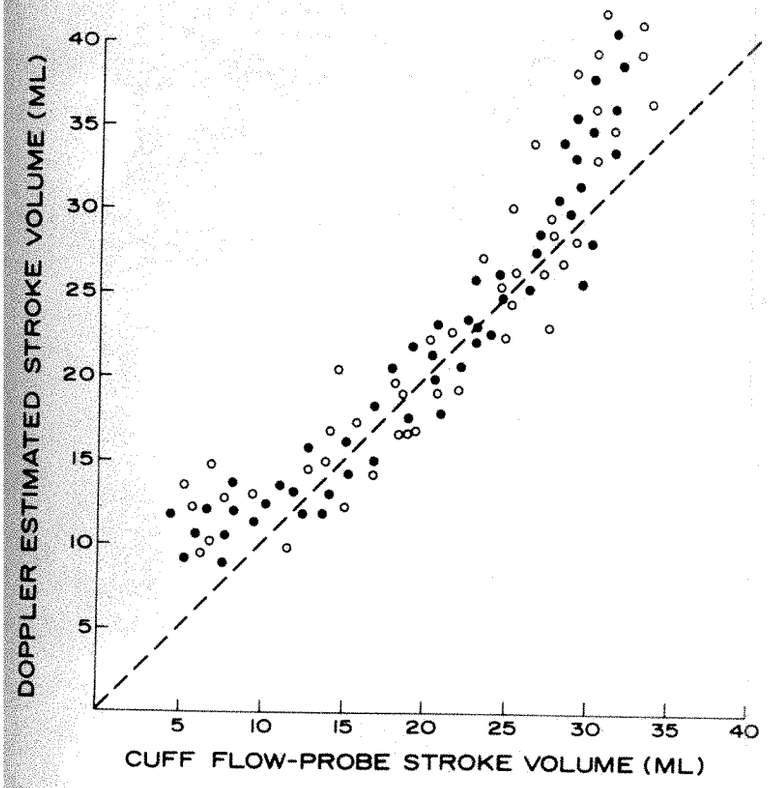


FIGURE 6. Comparison of stroke volumes (in ml) in one dog as measured by the Doppler technique and cuff flow probe. **Open circles** = transcutaneous probe; **closed circles** = juxta-aortic probe. To better demonstrate the differences encountered at very low and very high stroke volumes, correlation analyses were separated for the 5 to 15 ml, 15 to 25 ml and 25 to 35 ml range of stroke volumes. For 5 to 15 ml, the correlation coefficient (r) = 0.61, slope = 0.48, y intercept = 8.01, and the standard error of the estimate (SEE) = 3.3 ml; for 15 to 25 ml, r = 0.86, slope = 1.11, y intercept = −2.28 and SEE = 1.6 ml; for 25 to 35 ml, r = 0.77, slope = 1.78, y intercept = −19.12 and SEE = 4.3 ml.

Discussion

This study of 20 closed and open chest dogs demonstrated the usefulness of the method of estimating cardiac output by multiplying the 1 minute sum of Doppler velocity integrals in systole by the cross-sectional area of the proximal aorta. The method was accurate for estimating stroke volume in most hemodynamic situations except at extremely rapid heart rates and after an extrasystolic beat. We have also shown that Doppler signals recorded with the transducer outside the thoracic cage are almost identical to signals recorded with the probe 1 cm from the aortic wall, except for greater noise in the transcutaneous signal.

• **Physical and physiologic considerations:** There are theoretical reasons why a measurement of instantaneous blood flow velocity should parallel flow or cardiac output measurements by any other method. The forms of the velocity profile created by a pressure gradient that oscillates sinusoidally have been described in mathematical terms.[5] The pressure gradient is assumed to be the form $M \cos(\omega t - \psi)$, the standard expression for one harmonic component of a Fourier series. The equation

$$\frac{\partial U}{\partial t} = -\frac{1}{\rho}\frac{\partial p}{\partial \chi} + \nu\left(\frac{\partial^2 U}{\partial r^2} + \frac{1}{r}\frac{\partial U}{\partial r}\right)$$

describes the behavior of the axial (forward) velocity (U) as a function of the radius (r) of the vessel, time (t), the density of blood (ρ), and the kinematic viscosity (ν) when blood is subjected to an oscillatory pressure gradient. The geometric form of the oscillatory profile is well known[6] and helps to explain why problems in measurement arise in certain situations. The velocity at the aortic wall is zero (or near zero) and a boundary layer formed just distal to the aortic leaflets gradually grows in thickness until the flow in the entire aorta is influenced by this phenomenon of viscosity and the velocity distribution assumes a parabolic form. The flow velocity in the center of the aorta is then greater than at the aortic root in order to preserve continuity. The point at which this occurs is called the "inlet length" and changes throughout the cardiac cycle.[7] By taking velocity measurements from the proximal aorta, this problem of the parabolic profile is avoided, except at extremely low heart rates.

The equations that describe the characteristics of oscillatory flow in a tube are not precisely applicable to aortic flow because the aorta is distensible. The distensibility is complicated by (1) viscoelastic behavior that is responsible for attenuation of the pulse wave traveling from the heart, and (2) by a nonlinear response in resisting different degrees of arterial distension. However, the importance of this distensibility is more theoretical than functional, since Bernouilli's theorem: $p_o = p + \frac{1}{2}q^2\rho$ (where p_o is the uniform stagnation pressure of the flow, q is velocity, p is the hydrostatic pressure and ρ is the density of blood) relates pressure and velocity such that a flow curve (velocity curve) can be calculated from a pressure gradient measured in the proximal aorta.[8] This is particularly important because two of the three dimensions (cross-sectional area) we are using to calculate cardiac output have the capacity to change through systole, thus affecting the calculation of flow. Greenfield and Patel[9] have shown that the average change in aortic cross-sectional area during systole is 11 percent. In the dog aorta, the cross-sectional area is sufficiently small that the absolute error (in cm^2) would be acceptable for calculations of flow from area and linear velocity, particularly with the constraining effects of the cuff flow probe. However, in the human aorta, the area is larger (from 4.5 to 8.5 cm^2) and the pulse rate is slower than in the dog, so that absolute errors in area are much more important.

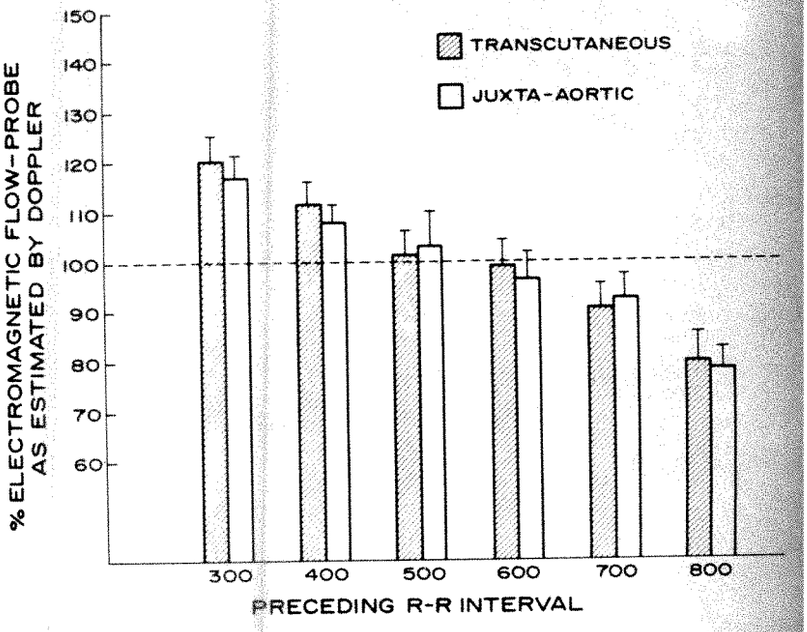


FIGURE 7. Graph depicting the percentage of flow probe stroke volume estimated by both Doppler probes at different preceding R-R intervals (in ms).

Clinical implications: If the method for estimating cardiac output and stroke volume using the integral of Doppler velocity signals during systole and the cross-sectional area of the aortic root is to be used in human studies, several factors must be considered: (1) a method for measuring the cross-sectional area of the aorta and accounting for systolic change will be required for accurate calculations; (2) in patients with multiple premature ventricular beats during the study, cardiac output calculated from Doppler velocity integrals will underestimate the true value; and (3) clinical situations associated with marked tachycardia may cause Doppler stroke volume estimations to be greater than the true value. These problems notwithstanding, the overall method appears to be extremely promising for clinical use.

Acknowledgment

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Transcutaneous Doppler Method of Measuring Cardiac Output—II

Noninvasive Measurement by Transcutaneous Doppler Aortic Blood Velocity Integration and M Mode Echocardiography

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In 15 patients with acute myocardial infarction (group I) and in 14 patients undergoing routine cardiac catheterization (group II) cardiac output values obtained by multiplying the 1 minute sum of the systolic integral of aortic blood flow velocity by the average systolic diameter of the aortic root were compared with values obtained with the thermodilution and Fick methods, respectively. Patients in group I were studied under various hemodynamic conditions, whereas those in group II were studied in the baseline state only. In group I, the correlation between the two methods was excellent (r values ranged from 0.96 to 0.99) except in one severely anemic patient whose Doppler signals were noisy, but at heart rates exceeding 150 beats/min it was not as good. In group II, the correlation between the two methods was r = 0.96 with a standard error of the estimate of 0.226 liter. The Doppler method is totally noninvasive and is useful for monitoring changes in cardiac output in patients with acute myocardial infarction.

A simple, accurate noninvasive method is needed for monitoring cardiac function in critically ill patients, particularly those with acute myocardial infarction. The state of the myocardium in these patients is in constant flux because of changing quantities of ischemic tissue and labile blood pressure and heart rate. Methods requiring a pulmonary arterial thermodilution catheter are hazardous in patients with coagulation abnormalities and are technically difficult in some situations. Echocardiography is a useful noninvasive method of assessing cardiac output but cannot be performed adequately in all patients. A noninvasive method for continuously monitoring hemodynamic data would be of considerable utility when administering antiarrhythmic agents, colloid and crystallized solutions, vasodilators and positive inotropic drugs.

Transcutaneous continuous wave Doppler measurements of aortic ejection velocity have been shown to approximate closely the velocity values obtained with invasive methods.[1,2] Relative changes in the integral of the velocity signal in systole have also been shown to correlate with changes in stroke volume over a wide range of cardiac output values in dogs.[3] Encouraged by these observations and by our own studies in dogs,[4] we investigated the possibility of using transcutaneous continuous wave Doppler ultrasound to measure absolute values of cardiac output in hemodynamically unstable patients with acute myocardial infarction, and in patients in stable condition undergoing diagnostic cardiac catheterization.

Methods

Patients

Group I—coronary care unit: Group I consisted of 12 men and 3 women (mean age 54, range 36 to 67 years) with acute myocardial infarction. All had historical, electrocardiographic and creatine kinase isoenzyme criteria for acute infarction and were studied in the coronary care unit of Grady Memorial Hospital or the Atlanta Veterans Administration Hospital. Materials required for studies

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in group I included a triple lumen flow-directed catheter (Edwards Laboratory), Edwards Laboratory digital thermodilution cardiac output computer (model 9510-A), 2 continuous-wave directional Doppler units (Sonicaid Corp; Bach-Simpson Ltd.) with 2.0 and 2.2 megahertz unfocused transducers and an Ampex multichannel instrumentation recorder.

Group II—cardiac catheterization laboratory: Group II consisted of 10 men and 4 women (mean age 50, range 32 to 58 years) undergoing diagnostic cardiac catheterization for chest pain in the Grady Memorial Hospital Cardiac Catheterization Laboratory. In group II the Doppler unit was connected to an eight channel recorder (Electronics for Medicine) with light-sensitive paper (Kodak® Linagraph). A Swan-Ganz flow-directed catheter and an angiographic pigtail catheter were placed in the pulmonary artery and thoracic aorta, respectively, to sample blood for the Fick determination.

Informed written consent was obtained from all 29 patients for the Doppler determination and for placement of the thermodilution pulmonary arterial catheter in group I and for the entire catheterization procedure with angiography in group II.

Cardiac Output Measurements

Determination of cardiac output standards: In group I the pulmonary arterial thermodilution catheter was inserted at the time of admission to the hospital. Cardiac output was determined by averaging the results of values obtained after three 10 ml bolus injections of dextrose in water cooled to 5° C.[5] These values were not known to the investigators until after all data were collected and the Doppler values calculated. In group II the Fick cardiac output was measured utilizing a 3 minute collection of expired gas (Douglas bag) analyzed for oxygen and carbon dioxide content using the Scholander technique, with simultaneous samples of anticoagulated blood drawn over a 90 second time period from the pulmonary artery (10 ml) and the aorta (10 ml). The pulmonary and systemic arterial whole blood oxygen contents were measured with the Van Slyke technique, and the arteriovenous difference was calculated by subtraction. Cardiac output (CO) was calculated using the standard formula:

$$CO\ (\text{liters/min}) = \frac{\text{Oxygen consumption (ml/min)}}{\text{Systemic arteriovenous oxygen difference (ml/liter)}}$$

Determination of aortic cross-sectional area: In each patient, an M mode echocardiogram of the aortic root and leaflets was performed before or during Doppler measurements (Fig. 1). Greenfield and Patel[6] showed that the average change in the cross-sectional area of the human proximal aorta during systole was 11 percent. We[7] have confirmed their observations using echocardiography as the method of measurement. Therefore, we used a method of determining the average systolic diameter from the aortic root echo, rather than merely using half the sum of end-diastolic and end-systolic diameters (Fig. 2). The average systolic cross-sectional area ($\bar{A}$) of the aortic root was calculated using the formula: $\bar{A} = \pi(\frac{1}{2}\bar{D})^2$ where $\bar{D}$ is the average aortic diameter.

Doppler velocity measurements: Doppler velocity measurements were made simultaneously with cardiac output determinations using the thermodilution technique in group I and during blood sampling in group II. For velocity measurements of blood flow in the proximal aorta, the continuous wave Doppler transducer was placed in the suprasternal notch and directed inferiorly toward the patient's left hip until a velocity signal was detected with peak flow toward the transducer. The transducer was rotated clockwise until the probe direction resulting in the greatest peak velocity (usually between 75 and 125 cm/s) was obtained. This method of aligning the probe was used in both groups. The reliability of obtaining nearly identical velocity tracings in the same patient was tested by removing the probe, replacing it, again locating the probe position resulting in the greatest peak velocity and comparing the signals. In each case there was less than 5 percent difference between the mean of 30 sequential values for peak velocity before and after the probe was moved.

Studies in the cardiac catheterization laboratory allowed further localization of the region of the proximal aorta from which Doppler velocity measurements were being made. Once the probe was aligned to detect maximal peak velocity, small quantities of contrast dye were injected into the proximal aorta under fluoroscopic control until the audio frequency produced by the Doppler instrument became lower in pitch and coarse in quality and coincided with the onset of dye ejection from the catheter. This region was always within 3 cm of the aortic root. Similar injections of dye into the brachiocephalic vessels were not detected with the Doppler instrument, indicating that subclavian and carotid flow velocities were not contaminating the aortic velocity measurements.

The Doppler shift frequencies detected with the ultrasonic probe were processed with a zero-crossing detector system and

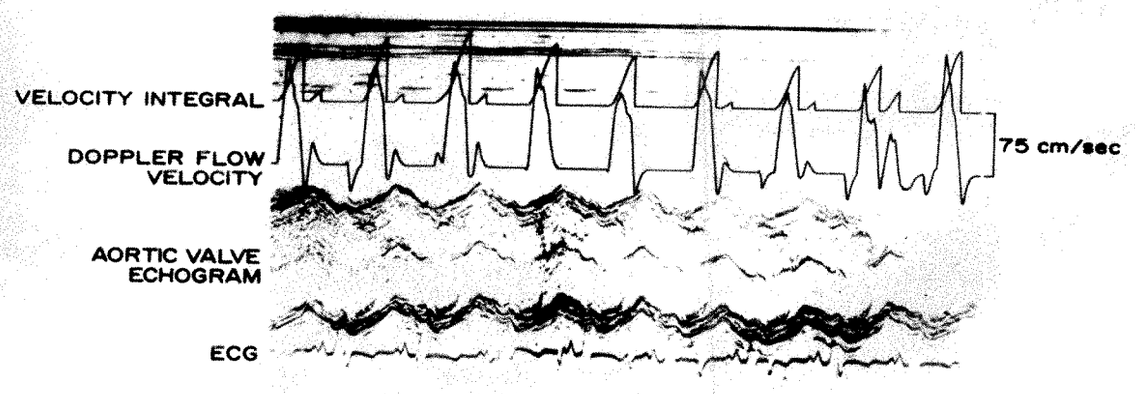


FIGURE 1. Simultaneous M mode echocardiogram of the aortic root, the aortic valve and continuous wave Doppler signals of flow velocity in the proximal aorta and electrocardiogram (ECG). The velocity integral is the electronic integration of the area beneath the systolic portion of the velocity signal above zero flow. The velocity integral (proportional to stroke volume) changes with respiration.

converted to an analog voltage signal. Zero flow (velocity) and signals of 50 and 100 cm/s were produced by the Doppler instrument electronically for calibration. Each raw velocity signal was recorded and simultaneously integrated to produce a signal that represented the area confined below each velocity curve and above zero flow. The electrocardiogram, velocity signal and velocity integral were recorded on an Electronics for Medicine eight channel recorder using light-sensitive paper (Kodak Linagraph), or were first recorded on a multichannel instrumentation recorder (Ampex®) and later replayed for permanent records.

Study protocol: In group I, velocity signals and thermodilution cardiac output values were measured soon after each patient was admitted to the coronary care unit. Depending on the baseline hemodynamic values (pulmonary capillary wedge pressure, heart rate and cardiac output), colloid solution, sodium nitroprusside or dopamine, or any combination, was infused at a rate commensurate with the needs of the patient. Thermodilution values and Doppler velocity measurements were obtained every 4 hours and each time a new drug was given or the rate of infusion was changed. An average of six comparisons between thermodilution cardiac output values and cardiac output values calculated from velocity signals were made in each patient.

In group II, the velocity signals were recorded during the Fick cardiac output determination. No hemodynamic agents were given.

Calculation of cardiac output from velocity signals: For each comparison between Doppler velocity signals and the cardiac output standard (thermodilution or Fick), the mean systolic cross-sectional area of the aorta was multiplied by the sum of all velocity integrals recorded during a 1 minute period. For example, if the mean systolic cross-sectional area was 7.0 cm^2, and the sum of velocity integrals recorded in 1 minute was 500 cm (the integral of velocity in cm/s over time gives a value with the dimensions of length), the calculated cardiac output would be 7.0 $cm^2 \times 500$ cm or 3,500 cm^3 (3.5 liters/min). Any integrals of velocity occurring in diastole were ignored in these calculations because diastolic "velocity" in the aorta represents the movement of blood that has already been ejected and therefore already measured.

Statistical analysis: The sequential values for calculated cardiac output determined from Doppler velocity signal integration and the echocardiographic mean aortic systolic cross-sectional area were compared with values measured with the thermodilution method separately in each patient in group I. Correlation analysis was used because comparison of data points between patients under different hemodynamic situations is not statistically valid. A correlation coefficient, slope, y intercept of the regression line and standard error of the estimate were computed for the series of measurements in each patient. In group II, cardiac output values were measured once in each patient in the baseline state only; a linear regression analysis was applied to the data in this group of patients.

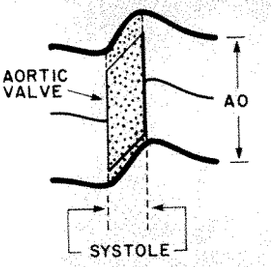


FIGURE 2. Diagram depicting the method of determining the average systolic diameter of the aortic (AO) root. The **shaded area,** which represents the time-integrated sum of all instantaneous systolic diameters, is measured with planimetry and then divided by the systolic ejection time to obtain the average diameter.

Results

Group I—coronary care unit: Velocity signals were obtainable in all 15 patients; they were reproducible during any one period of measurement and were generally smooth and uniform in shape. The time required to locate the probe position that produced the maximal peak velocity averaged 60 seconds; the longest time required was 2 minutes, 15 seconds in a patient who initially would not lie still.

During the infusion of dopamine at the rate of 14 μg/kg per min in one patient, the velocity signal was rough, presumably because of the associated pulse rate of 156 beats/min. At lower infusion rates, the problem

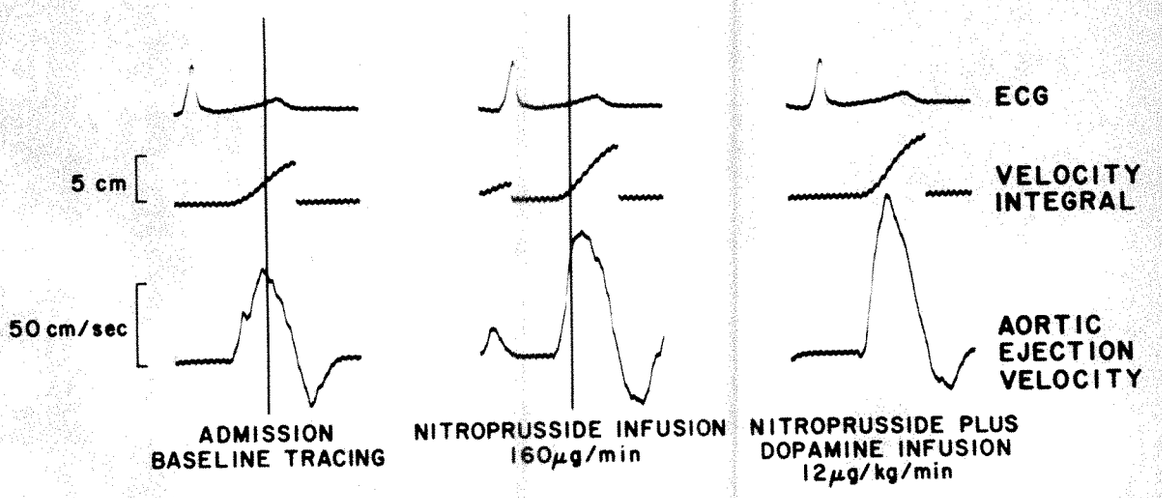


FIGURE 3. Patient C. The electrocardiogram (ECG), velocity integral and aortic ejection velocity are shown at the time of admission, 4 hours later with nitroprusside infusion, and 8 hours later with both a dopamine and a nitroprusside infusion. Both the peak velocity and the velocity integral increased after a single intervention and then after combined pharmacologic interventions.

was not encountered. A similar problem occurred in a severely anemic patient before transfusion and in a febrile patient before the body temperature was lowered. Figure 3 is a representative tracing showing the velocity signals recorded from one patient under three hemodynamic conditions. The comparison of calculated and measured cardiac output values for each patient is shown in Figure 4, and further details are given in Table I. There was generally an excellent correlation between the two methods except in Patient D, who was anemic (hematocrit = 22 percent) and had marked tachycardia (more than 160 beats/min) during all measurements. The standard error of the estimate ranged from 0.004 liter to 0.129 liter in these 15 patients.

Group II—cardiac catheterization laboratory: Velocity signals obtained in group II were also smooth and of uniform size and shape. All patients had a heart rate at rest of less than 100 beats/min, a hematocrit value greater than 35 percent and a basal body temperature of less than 38° C. Fick cardiac output values and those calculated from velocity signals are compared in Figure 5. The correlation coefficient, slope, intercept and standard error of the estimate are given in the figure legend; however, additional (and perhaps more practical) information is shown in the figure itself by the two curved lines that represent the 95 percent confidence limits for measurements in each cardiac output range. The distance between the lines of each point on the abscissa is therefore a function of the predictive value of the Doppler method under these conditions and in this laboratory. Although the confidence limits were wider at low and high cardiac output values, the error of the Doppler estimation was only 0.3 liter at the highest cardiac output value and only 0.2 liter at the lowest level of cardiac output. Thus, even at the two extremes of the curve, the accuracy of the Doppler method is sufficient for clinical use.

Conditions producing Doppler signals with a low signal to noise ratio: We noted three situations that seemed to produce rough velocity signals with considerable noise: (1) fever (temperature more than 39° C), (2) anemia (hematocrit less than 26 percent), and (3) rate of dopamine infusion (more than 14 μg/kg per min). Further evaluation revealed a common factor; the heart rate in each situation was more than 150 beats/min. This was best demonstrated in two patients with noisy signals receiving dopamine infusions of 16 and 18 μg/kg per min and with heart rates of 172 and 158 beats/min, respectively. When the infusion rate was lowered to 12 μg/kg per min, the heart rate in both patients decreased to less than 150/min. Velocity signals became much less noisy, uniform in shape and of smooth configuration. The same sequence of events occurred in the patients with fever or anemia in whom signal noise almost disappeared when these problems were treated. Values in Patient A (Fig. 4) represent measurements made after the fever was eliminated. However, in Patient D, the measurements were made while the patient was still anemic because matched blood was not available for 48 hours.

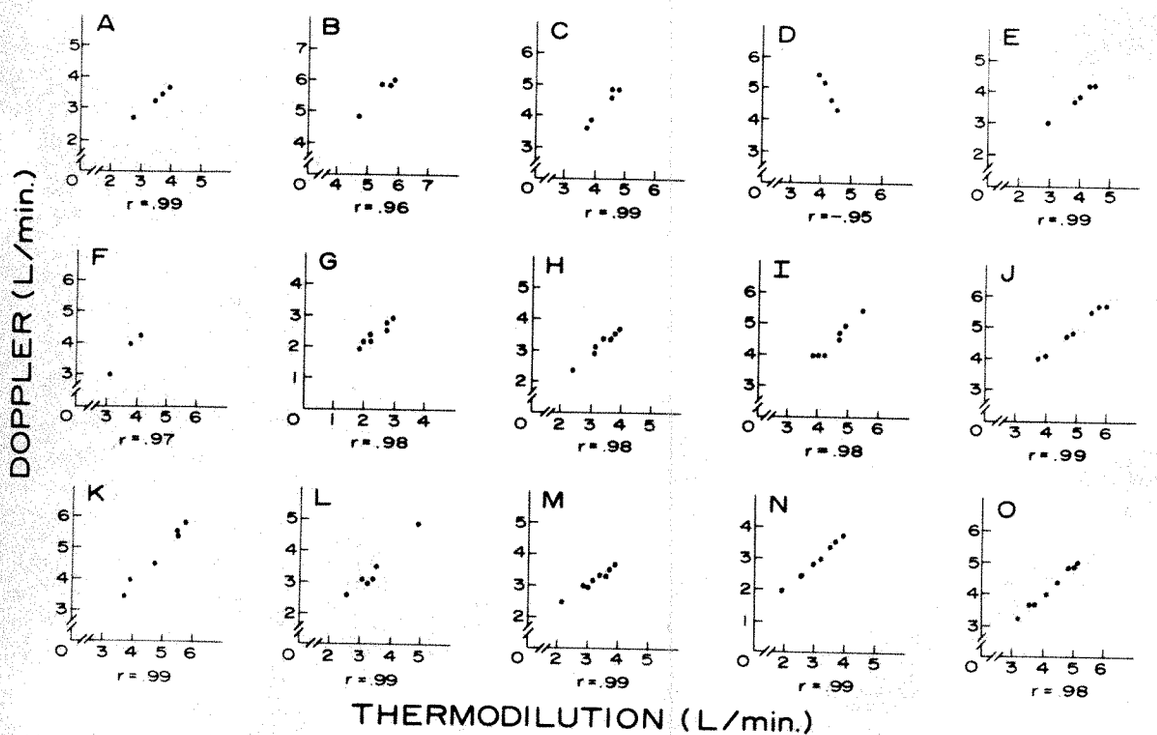


FIGURE 4. Linear regression plots of cardiac output values calculated from the Doppler velocity signals versus simultaneous values obtained with thermodilution in 15 patients (group 1). The correlation coefficient for each patient is shown below each plot. These values were obtained at the time of admission (usually the lowest value), and during dopamine or nitroprusside infusion, or both.

Discussion

Light[8] first described the application of the Doppler principle for the noninvasive measurement of instantaneous blood velocity in the proximal aorta of human subjects. The wave forms he obtained were similar to those established with invasive flow probe techniques. He described the method of placing the transducer in the suprasternal notch to record flow patterns in the aorta. The development of a direction-resolving circuit that introduced a phase shift before detection made possible the identification and separation of positive and negative Doppler shifts, that is, forward and backward flow.[9] Huntsman et al.[10] recorded aortic blood flow velocities in human subjects and obtained reproducible patterns from both the ascending aorta and the aortic arch.

The transcutaneous Doppler method has also been used to assess relative changes in stroke volume. Colocousis et al.[3] demonstrated that continuous wave Doppler ultrasound could estimate stroke volume changes in dogs subjected to several hemodynamic interventions that caused cardiac output to vary over a wide range. These investigators demonstrated a close correlation between the integral of the velocity signal and stroke volume as measured with standard thermodilution techniques. Studies in our laboratory[4] have confirmed their observations.

Clinical application: The results of previous studies using the Doppler method in both animals and human beings, plus the results of this study in patients, clearly demonstrate the potential of this procedure in the initial evaluation and hourly monitoring of patients whose condition is hemodynamically compromised. In previous reports[1,3,8,10] relative changes in blood velocity or stroke volume were assessed without assigning actual quantitative units to the results. Our study demonstrates that in many patients cardiac output (in liters/

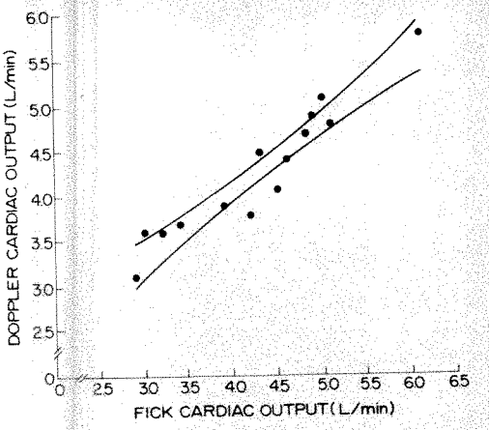


FIGURE 5. Cardiac output values obtained with the Fick and Doppler methods are plotted for each of the 14 patients in group II. The two lines represent the 95 percent confidence limits for the equation: $y = a + bx$, where y = Fick value, a = 1.02, b = 0.76, and x = measured Doppler value for cardiac output. The correlation coefficient for the regression line is 0.96 and the standard error of the estimate is 0.226 liter.

TABLE I

Clinical Data, Cardiac Output Values, and Statistical Correlations Between Thermodilution and Doppler Values in Group I

Case	Hct (%)	Temp (°C)	Site of Infarct	Aortic Root Area (cm^2)	Initial PCWP (mm Hg)	Cardiac Output (liters/min) Initial T	Initial D	Final T	Final D	Correlation (r value)*	SEE (liters)	p Value	Other Clinical Data
A	34	40.0	Inf	6.1	4	2.8	2.6	3.6	3.3	0.99 (n = 5)*	0.004	0.00001	Septic shock
B	48	36.2	Ant	5.9	19	4.8	4.9	6.1	5.9	0.96 (n = 5)	0.140	0.00520	IHSS
C	42	37.6	Ant	5.7	24	3.8	3.6	4.6	4.8	0.99 (n = 5)	0.063	0.00017	Pulmonary edema
D	24	36.0	Ant	7.0	4	4.2	5.3	4.4	4.6	−0.95 (n = 5)	0.141	0.00633	Gastric bleeding
E	45	38.4	Ant	4.9	20	4.0	3.8	4.1	3.9	0.99 (n = 5)	0.036	0.00001	. . .
F	39	37.0	Ant	6.6	22	3.1	3.0	4.0	3.9	0.97 (n = 5)	0.111	0.01238	. . .
G	34	38.2	Ant	8.5	29	2.9	3.0	1.9	2.0	0.98 (n = 7)	0.078	0.00004	Hypotension, death
H	45	37.1	Ant	7.5	26	2.4	2.5	3.6	3.6	0.98 (n = 8)	0.065	0.00001	Ventricular aneurysm
I	43	37.4	Lat	8.0	12	4.8	4.8	5.4	5.6	0.98 (n = 7)	0.105	0.00002	. . .
J	51	37.8	Inf	7.0	4	3.9	4.0	5.8	5.7	0.99 (n = 8)	0.091	0.00001	Volume depletion
K	39	38.0	Inf	4.9	9	3.9	3.7	5.8	5.8	0.99 (n = 6)	0.116	0.00004	Tricuspid regurgitation
L	36	36.5	Post	5.3	14	3.1	3.2	5.0	4.8	0.99 (n = 6)	0.103	0.00005	. . .
M	41	37.6	Lat	6.6	32	2.2	2.6	2.0	2.1	0.99 (n = 11)	0.109	0.00001	Peripheral vasoconstriction
N	44	37.4	Ant	6.6	31	1.9	2.0	4.0	3.8	0.99 (n = 7)	0.046	0.00001	Cardiogenic shock
O	39	37.2	Ant	4.9	23	3.2	3.3	5.1	5.0	0.98 (n = 8)	0.124	0.00001	Pulmonary edema

* n refers to the number of observations in that patient.

Ant = anterior; D = Doppler; Hct = hematocrit; IHSS = idiopathic hypertrophic subaortic stenosis; Inf = inferior; Lat = lateral; PCWP = pulmonary capillary wedge pressure; p = probability; Post = posterior; SEE = standard error of the estimates; T = thermodilution; Temp = rectal temperature.

min) can be determined with a sufficiently small error to be useful in clinical practice.

In most patients the velocity profile in the proximal aorta is almost flat over most of its cross section and reproducible results are not critically dependent on the aim of the ultrasonic beam if its direction is approximately tangential to the course of the vessel.[11] The basic Doppler equation, $v = \Delta fc/2f_0\cos\theta$,* indicates that flow velocity can be calculated from the observed Doppler shifts with an accuracy of ±10 percent if the beam is within 25° of the direction of flow because of the small variation of $\cos\theta$ when θ is near 0. For the measurement of volume flow (Q), the Doppler equation must be multiplied by the cross-sectional area (A) of the vessel: $Q = (A)\ (\Delta fc)/(2f_0\cos\theta)$. The mean frequency shift (Δf) in this case is the average over the total vessel lumen; and θ is the average angle over the total lumen.

*c = sound velocity; f = the Doppler shift (Hz); f_0 = the center frequency (Hz); θ = the angle between the beam vector and velocity; and v = flow velocity.

Advantages: The Doppler method has several advantages over catheterization techniques for the repeated measurement of cardiac output: (1) A single unit can be used on multiple patients; (2) it carries none of the risks of indwelling catheters; (3) it does not require blood samples (as does the Fick method) or expansion of the intravascular volume (as does the thermodilution technique) that may present problems when serial studies are performed; and (4) the technique can be learned and used with accuracy and safety not only by cardiologists and cardiovascular surgeons, but also by nurses and technicians.

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Improved Diagnostic Accuracy of Thallium-201 Stress Test Using Multiple Observers and Criteria Derived From Interobserver Analysis of Variance

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This study was performed to determine the interobserver variance for the interpretation of segmental thallium-201 image scores and the changes in such scores between the exercise and delayed images. Fifty patients, 40 with and 10 without significant coronary artery disease, underwent thallium imaging immediately after exercise and 2 hours later in the anterior and 50° left anterior oblique projections. The left ventricle was divided into six segments and graded by four independent observers on a scale of 0 (minimal activity) to +2 (normal activity). Interobserver variance was determined for each segment. For a change in thallium activity between exercise and delayed images, the interobserver variance was greatest for the apical and apical-inferior segments, intermediate for the inferior and septal segments and least for the anterolateral and posterior segments.

When segmental thallium scores were interpreted by an individual observer using a standard method employing one set of arbitrary criteria (method 1), the thallium stress test had a sensitivity of 77 percent and a specificity of 75 percent for coronary artery disease. When the scores were interpreted by an individual observer using criteria derived from interobserver variance analysis (method 2), the sensitivity increased to 86 percent (probability [p] <0.05); the specificity (78 percent) did not change significantly. When multiple observers arrived at a single diagnosis by consensus (method 3), the sensitivity was 75 percent and specificity 90 percent. However, when the multiple observers' scores were averaged and the averaged scores interpreted by a single set of criteria applied to all six ventricular segments (method 4), the sensitivity and specificity increased to 90 percent ($p < 0.05$ and not significant, respectively [method 4 versus method 1]). Thus, there is considerable interobserver variance in the qualitative scoring of segmental thallium activity. More caution must be observed in interpreting changes in activity from exercise to delayed images in the apical and apical-inferior segments than in the anterolateral and posterior segments. When only one observer is available, diagnostic accuracy is improved by using criteria based on interobserver variance analysis. However, when feasible, thallium stress tests should be interpreted by multiple observers because averaging of the multiple observers' scores maximizes both sensitivity and specificity.

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Exercise thallium-201 myocardial perfusion imaging has been used extensively for the diagnosis of coronary artery disease.[1-9] Pohost et al.[10] demonstrated the resolution of some defects present on initial postexercise thallium images when patients underwent further imaging several hours after a single dose of thallium. Exercise image defects that disappeared were believed to represent transient ischemia whereas defects that persisted were thought to represent scar. Despite the increasing use of thallium myocardial imaging, the interobserver variability in the

qualitative assessment of thallium activity has not been well defined. Trobaugh et al.[11] demonstrated the effect of this interobserver variance on the overall interpretation of the thallium study. Thus, the precision and diagnostic accuracy of these tests depends on this variability. Furthermore, because a consensus interpretation by multiple observers has been used in most studies of the diagnostic accuracy of the thallium stress test for coronary artery disease, the diagnostic accuracy for a single observer remains to be determined. This study was undertaken (1) to determine the interobserver variance in the qualitative scoring of segmental thallium myocardial activity, (2) to determine the diagnostic accuracy of a single observer's interpretation of thallium stress and delayed images, and (3) to evaluate the usefulness of several techniques designed to minimize the loss of diagnostic accuracy due to interobserver variance.

Methods

Study patients: The study group consisted of 50 patients (40 men and 10 women) who had thallium stress tests ordered by their private physicians for the evaluation of chest pain, and who subsequently underwent cardiac catheterization. Their mean age was 54 ± 9 (standard deviation) years (range 31 to 66).

All patients had selective coronary angiograms recorded with 35 mm cinematography at 60 frames/s. The angiograms were interpreted by two observers who arrived at a consensus diagnosis without knowledge of the results of thallium imaging. Significant coronary artery disease was defined as 50 percent or greater narrowing of at least one major coronary artery in at least two projections. Forty patients had significant coronary artery disease and 10 did not. Thallium stress tests were performed within 1 week of cardiac catheterization.

Thallium-201 image acquisition: Before exercise, a supine 12 lead electrocardiogram was obtained and an intravenous cannula was placed in a dorsal hand vein. Patients were stressed in the supine position with use of a bicycle ergometer. We routinely use either supine bicycle or treadmill exercise for thallium stress tests at our institution and have found no difference in the diagnostic accuracy of the two techniques.[3,9] Supine exercise was used in this study so that imaging could be initiated immediately after the end of exercise. Electrocardiographic lead II was monitored continuously and selected leads were recorded at 2 minute intervals. The initial exercise work load was 150 kilopond-meters (kpm)/min and increased by 150 kpm/min every 2 minutes. Exercise was symptom-limited by chest pain, shortness of breath or leg fatigue. Approximately 30 to 60 seconds before the anticipated completion of exercise, 1.5 mCi of thallium-201 (New England Nuclear, North Billerica, Massachusetts) was injected intravenously. Immediately after the completion of exercise and 2 hours later, imaging was performed with the patient supine in the anterior and 50° left anterior oblique projections.

Images were obtained with a conventional Anger scintillation camera (Ohio Nuclear Series 420 Mobile Gamma Camera) interfaced with a mobile nuclear medicine computer system (MUGA-CART, Medical Data Systems, Ann Arbor Michigan). An all purpose, medium resolution collimator was used. A 30 percent energy window encompassing X-ray emissions at 60 to 80 keV was selected. Imaging time for each collection was 6 minutes. Data were collected in a 128 by 128 matrix-byte mode format.

Thallium-201 stress test: data analysis: The thallium images were viewed on a computer gray scale display for interpretation. Only the central portion of the thallium image containing the myocardium was displayed. The exercise and delayed images were displayed side by side for comparison. No other computer manipulations were performed. Each image was interpreted by four independent observers unaware of the patient's cardiac catheterization findings or clinical history. The ventricle was divided into anterolateral, apical and inferior segments in the anterior view, and septal, apical-inferior and posterior segments in the 50° left anterior oblique view (Fig. 1). These segments were believed to correspond to the distribution of the three coronary arterial systems.

Thallium activity in each segment was subjectively graded as 0, 0.5, 1.0, 1.5 or 2.0. For each image, the segment (or segments) that demonstrated the most intense and homogeneous thallium activity (that is, the most normal) was graded +2. Segments that demonstrated no activity were graded 0. Segments that demonstrated clearly reduced, yet not absent activity were graded +1. Segments demonstrating decreased transmural thickness compared with the normal segment were also graded +1, except for the apical, septal, and apical-inferior segments which can normally appear thin. Larger apical and apical-inferior defects were considered normal in ventricles believed to be dilated. Half-points in the scoring system were used when an observer thought that activity or thickness of a segment was intermediate between two grades.

Four methods for interpretation of scores were studied. These methods are summarized in Table I and are further explained as follows:

Method 1 (individual observer, standard criteria): Individual observers' scores were first interpreted using the following (standard) criteria: A transient defect was defined as an increase in grade of 1.0 or more from the exercise to delayed image for any of the six ventricular segments. If a defect in the anterolateral, inferior, septal or posterior segment was present

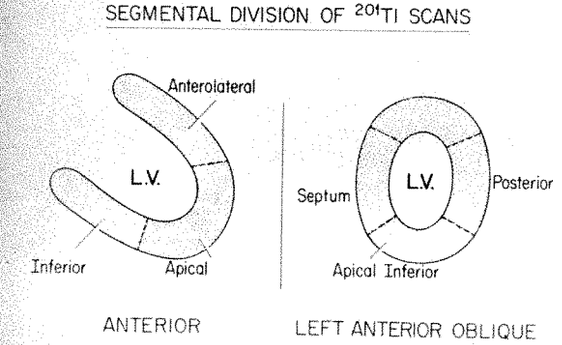


FIGURE 1. Schematic drawing demonstrating segmental division of thallium-201 images. L.V. = left ventricle.

TABLE I

Methods Used for Interpretation of Segmental Thallium-201 Image Scores

Method	Observers	Criteria Used
1	Individual	Standard
2	Individual	Interobserver variance analysis
3	Multiple (four) (consensus)	Standard
4	Multiple (four)	Average

at exercise (grade 1.0 or less) but did not increase by a grade of at least 1.0, it was considered a persistent defect. If a defect in the apical or apical-inferior segment was present at exercise (grade 0.5 or less), but did not increase in grade by at least 1.0, it was considered a persistent defect because these segments normally have less activity than that in the other four segments.

Method 2 (individual observer, interobserver variance analysis criteria): Interobserver variance analyses were performed for the six segments. On the basis of these results, criteria for the interpretation of segmental thallium scores were derived for each of the six ventricular segments (interobserver variance analysis criteria, Table II). Individual observers' scores were reinterpreted using these criteria.

Method 3 (multiple observers by consensus): The four individual observers' scores were used to arrive at a single interpretation for each patient by consensus. If at least three of four observers agreed on the presence of a defect, then the consensus was judged positive for coronary artery disease. Otherwise, the consensus was considered negative for coronary artery disease. The standard criteria were used for this analysis.

Method 4 (multiple observers, average criteria): The four observers' scores were averaged to yield a multiobserver score for each segment. These scores were interpreted using the following arbitrarily derived set of criteria (average criteria), which allowed smaller changes in scores to be considered significant than those of the standard criteria: A transient defect was defined by an increase in score of 0.5 or greater from the exercise to delayed image for any of the six ventricular segments. If a defect in the anterolateral, inferior, septal or posterior segment was present at exercise (grade 1.5 or less) but did not increase by a grade of at least 0.5, it was considered a persistent defect. If a defect in the apical or apical-inferior segment was present at exercise (grade less than 0.75) but did not increase by at least 0.5, it was considered a persistent defect because these segments normally have less activity than the other four segments.

With all four methods, a thallium stress test with at least one transient or persistent defect was considered positive for coronary artery disease.

Statistical analysis: Differences between the four individual observers' segmental scores and changes in these scores between exercise and delayed images were analyzed by a two-way analysis of variance. For the purpose of this study, the total estimated interobserver variance was defined as the error due to observer bias plus the random error inherent in the method. We expressed the estimated interobserver variance (s_{IO}^2) in terms of its associated standard deviation, that is, as $2 \times s_{IO}$ where the factor of 2 was chosen to give an approximate 95 percent confidence limit.[12] Variances were compared using an F test.

The sensitivity and specificity of the thallium stress test were defined as follows:

$$\text{Sensitivity} = \frac{\text{True positive tests}}{\text{True positive tests} + \text{False negative tests}}$$

$$\text{Specificity} = \frac{\text{True negative tests}}{\text{True negative tests} + \text{False positive tests}}$$

Sensitivity and specificity were calculated for each observer and then averaged to yield an overall sensitivity and overall specificity for the methods using individual observers. Sensitivity values for the four methods were compared by estimating the variance of the difference of these values with the use of a table of correlated proportions.[13] Each difference in sensitivity was then divided by the square root of this estimated variance (that is, by the estimated standard deviation of the difference in sensitivity values) to obtain a standard normal z variate. This z variate was then referred to a table of the cumulative normal distribution (area under both tails) to test the null hypothesis that the pair of sensitivity values were equal. The probability that the two values for sensitivity were equal, given the estimated z variate, was the conventional probability (p) value. Specificity values for the four methods were compared in the same manner.

Results

Interobserver variance in the scoring of segmental thallium-201 activity: Figures 2 and 3 demonstrate the interobserver variance in the scoring of segmental thallium activity for the exercise and delayed images and for the change in grade between the exercise and delayed images, respectively. The variance values were significantly higher for all exercise image segments ($p < 0.01$) than for corresponding delayed image segments, except for the apical segment. Those for the

TABLE II

Criteria for Interpretation of Segmental Thallium-201 Scores (scoring system from 0 to +2) Derived From Interobserver Variance Analysis

Interpretation	Left Ventricular Segment					
	AL	AP	Inf	Sep	AI	Post
Transient defect	$\Delta \geq 0.5$	$\Delta \geq 1$	$\Delta \geq 1$	$\Delta \geq 1$	$\Delta \geq 1$	$\Delta \geq 0.5$
Persistent defect*						
Exercise	≤ 1	$=0$	≤ 1	≤ 1	$=0$	≤ 1
Delayed	≤ 1.5	≤ 0.5	≤ 1.5	$\leq 1^{\dagger}$	≤ 0.5	≤ 1.5

* The criteria for a persistent defect require that conditions for both the thallium-201 image immediately after exercise (Exercise) and the image obtained 2 hours later (Delayed) be satisfied.

† Includes a delayed image score of 1.5 if the exercise image score is 1.

AI = apical-inferior; AL = anterolateral; AP = apical; Inf = inferior; Post = posterior; Sep = septal; Δ = exercise minus delayed image score.

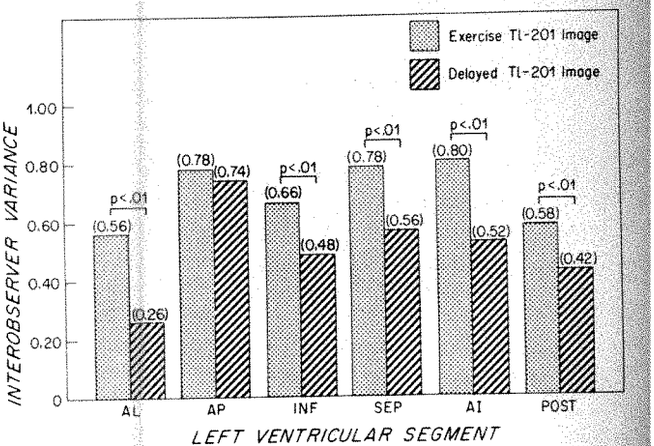


FIGURE 2. Interobserver variance in the scoring of left ventricular segmental thallium-201 (TL-201) activity for exercise and delayed images, expressed as 2 standard deviations (scoring system from 0 to +2). Left ventricular segments are anterolateral (AL), apical (AP), inferior (INF), septal (SEP), apical-inferior (AI), and posterior (POST). Comparisons among segments are discussed in text.

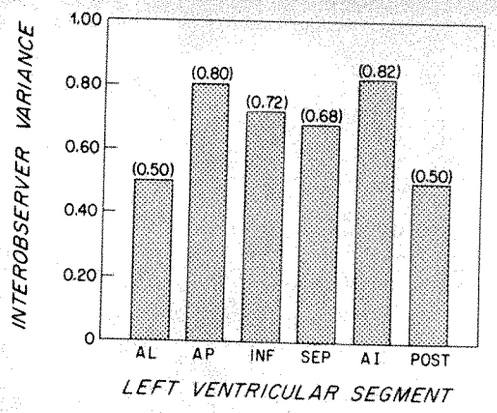


FIGURE 3. Interobserver variance in the scoring of changes in left ventricular segmental thallium-201 activity in exercise and delayed images, expressed as 2 standard deviations (scoring system from 0 to +2). Left ventricular segments as in figure 2. Comparisons among segments are discussed in text.

anterolateral and posterior segments in the exercise image were significantly lower ($p < 0.05$) than those for the other exercise image segments. The variance for the anterolateral segment in the delayed image was lower ($p < 0.01$) and that for the apical segment higher ($p < 0.01$) than that for all other delayed image segments. The variance values for a change in score between exercise and delayed images were lower for the anterolateral and posterior segments ($p < 0.01$) than for all other segments, and higher for the apical and apical-inferior segments ($p < 0.01$) than for all other segments except the inferior segment.

Table II lists the set of criteria (interobserver variance analysis criteria) for the interpretation of thallium scores derived from the interobserver variance values in Figures 2 and 3. For example, because the interobserver variance for change in thallium activity from an exercise to a delayed image is 0.5 for the anterolateral segment (Fig. 3), the interobserver variance analysis criteria require a difference in anterolateral exercise minus delayed image score (Δ) to be at least 0.5 for significance at the 95 percent confidence level. In this manner, the criteria have been individualized for each ventricular segment. The individual observers' scores were then reinterpreted using the interobserver variance analysis criteria (method 2) instead of the standard criteria (method 1). For example, one patient had an exercise anterolateral segment grade of 1.5 and a delayed anterolateral segment grade of 2.0. With use of the standard criteria, the anterolateral segment was interpreted as normal because a change in score of at least 1.0 was required for a transient defect. When these scores were reinterpreted using the interobserver variance analysis criteria, the anterolateral segment was interpreted as abnormal demonstrating a transient defect, because the change in score was at least 0.5.

TABLE III

Detection of Coronary Artery Disease With Thallium-201 Stress Test: Sensitivity and Specificity Using Four Methods of Interpretation

	Sensitivity (%)	Specificity (%)
Individual observer		
1. Standard criteria (method 1)	77	75
2. Interobserver variance analysis criteria (method 2)	86	78
		$p < 0.05$
Multiple observer		
1. Consensus* (method 3)	73	90
2. Average criteria (method 4)	90	90

* Three of four positive interpretations required for positive diagnosis.

Observer agreement in the overall interpretation of the thallium-201 stress test: *Method 1 (individual observer, standard criteria):* When the four observers' scores were individually interpreted using the standard criteria, the number of times that the observers agreed on the diagnosis regardless of the correct diagnosis was determined. There was complete observer agreement (four of four observers) in 29 (58 percent) of the 50 cases, partial observer agreement (three of four observers) in 13 cases (26 percent) and complete observer disagreement (two of four observers) in 8 cases (16 percent).

Method 2 (individual observer, interobserver variance analysis criteria): When the four observers' scores were individually interpreted using the interobserver variance analysis criteria, there was complete observer agreement in 35 (70 percent) of the 50 cases, partial observer agreement in 11 (22 percent) and complete observer disagreement in 4 (8 percent). The improved observer agreement using the interobserver variance analysis criteria compared with the standard criteria did not reach statistical significance (chi square = 2.06).

Sensitivity and specificity of thallium-201 test for coronary artery disease: Table III lists the sensitivity and specificity for coronary artery disease of the thallium stress test using the four different methods of interpretation.

Method 1 (individual observer, standard criteria): For an individual observer using the standard criteria, the overall sensitivity was 77 percent and the overall specificity 75 percent for coronary artery disease.

Method 2 (individual observer—interobserver variance analysis criteria): When the interobserver variance analysis criteria listed in Table II were applied to the individual observers' scores, the overall sensitivity increased to 86 percent ($p < 0.05$ compared with method 1). The overall specificity increased slightly to 78 percent (p = not significant compared with method 1).

Method 3 (multiple observers by consensus): When four observers used the standard criteria and arrived at a single diagnosis by consensus (three of four positive scores required for a positive diagnosis) the sensitivity was 73 percent and specificity 90 percent. These values were not statistically different from the values obtained with method 1.

Method 4 (multiple observers, average criteria): When the multiple observers' scores were averaged and the average scores interpreted with the average criteria, the sensitivity increased to 90 percent ($p < 0.05$ compared with method 1). The specificity also increased to 90 percent, although the difference from the value ob-

tained with method 1 was not statistically significant. Of the 40 patients with coronary artery disease, 9 had a transient defect alone, 8 had a persistent defect alone and 19 had both a transient and a persistent defect. Of the 10 patients without coronary artery disease, 1 had a transient defect, and none had either a persistent defect or both a transient and a persistent defect.

Discussion

Thallium myocardial perfusion imaging at rest has been used most extensively for the evaluation of patients with acute myocardial infarction,[14–18] unstable angina[19] and angina due to coronary arterial spasm.[20] Exercise thallium imaging has been used extensively for the diagnosis of coronary artery disease.[1–9] The precision of thallium imaging in diagnosing cardiac disease is dependent on interobserver variance in scoring and interpretation.

Interobserver variance in the scoring of segmental thallium-201 activity: Our results demonstrate the interobserver variance in the scoring of segmental myocardial thallium activity on exercise and delayed images. The values presented in Figures 2 and 3 represent estimated interobserver variance expressed as 2 standard deviations, which represent approximate 95 percent confidence levels for scoring thallium activity. Thus, the subjective grading of delayed image segmental thallium activity using a scoring system ranging from 0 to +2 is precise to within a grade of ± 0.26 to ± 0.74 depending on the segment analyzed (Fig. 2). Subjective scoring of exercise segmental thallium activity is precise to within a grade of ± 0.56 to ± 0.80 depending on the segment analyzed. The change in score between the exercise image and the delayed image is precise to within a grade of ± 0.50 to ± 0.82 depending on the segment analyzed (Fig. 3). Changes of less than these magnitudes fall within the range of interobserver variance and cannot be interpreted at the 95 percent confidence level. The higher variance values for the apical and apical-inferior segments are probably due to the wide spectrum of normal for these segments, because these segments can normally have decreased activity due to myocardial thinning. The overall lower variance values of the anterolateral and posterior segments compared with those of the inferior and septal segments may be due to higher target to background ratios for the first two segments. The outer edges of the anterolateral and posterior segments border the lungs, which have relatively low activity, whereas the outer edges of the inferior and septal segments border the right ventricle, which has relatively high activity.

Variance values were significantly higher for all exercise image segments (exept for the apical segment) than for corresponding delayed image segments. One explanation for this finding may be that the majority of defects were present in the exercise images, because many of them disappeared by the time of the delayed images. Thus, a greater proportion of the delayed images were completely normal and easier to score. Another explanation may be related to the increase in the background lung activity that occurs with exercise in some patients with coronary artery disease. This increased lung activity essentially disappears by the time of the delayed image. The decreased target to background ratio results in a reduction in image contrast in the exercise thallium image.

Observer agreement in the overall interpretation of thallium-201 stress tests: Our results demonstrate considerable interobserver variance in the overall interpretation of the thallium stress test. When the standard criteria and four observers were used, there was complete agreement on the overall diagnosis in 58 percent, partial agreement in 26 percent and complete disagreement in 16 percent of cases. Use of the interobserver variance analysis criteria increased complete agreement to 70 percent and decreased partial agreement and complete disagreement to 22 and 8 percent, respectively.

Other investigators have demonstrated considerable interobserver variance in the interpretation of the thallium stress tests. Trobaugh et al.,[11] using four observers, demonstrated "essentially complete" agreement on the overall diagnosis when the thallium images were interpreted twice by different observers. Lenaers et al.[1] using two observers, reported disagreement on the presence or absence of "hypoperfusion" in 7.5 percent of segments. Finally, Bailey et al.,[6] using two observers, reported disagreement on the significance of a change from exercise to rest in 14 percent of patients.

Sensitivity and specificity of the thallium-201 stress test for coronary artery disease: Our results demonstrate a sensitivity of 77 percent and a specificity of 75 percent for the thallium stress test in the detection of coronary artery disease when an individual observer uses the standard criteria (method 1). When an individual observer uses separate criteria derived from an interobserver variance analysis for each of the ventricular segments (method 2), the sensitivity increases to 86 percent ($p < 0.05$) with no significant change in specificity (78 percent). The increased sensitivity is accompanied by an increase in observer agreement and a decrease in observer disagreement. Thus, the use of criteria derived from an interobserver variance analysis allows for more sensitive interpretation of small changes in thallium activity scores without an attendant decrease in specificity.

When four observers used the standard criteria and arrived at a single diagnosis by consensus (method 3), the sensitivity was 75 percent and specificity 90 percent. Most previously reported studies have used the consensus interpretation of two to four observers and have reported similar values for sensitivity (range 56 to 95 percent) and specificity (range 88 to 97 percent).[1–8] In the present study, when the multiple observers' scores were averaged and the averaged scores interpreted by the average criteria (method 4), the sensitivity increased to 90 percent ($p < 0.05$) and the specificity remained at 90 percent. Thus, interpretation by multiple observers increases the diagnostic accuracy of the thallium stress test, possibly by averaging out isolated false diagnoses by individual observers.

Implications: There is considerable interobserver variance in the qualitative scoring of segmental thallium myocardial activity. This variance is particularly high

for scoring changes in activity between exercise and delayed images for the apical and apical-inferior segments. Thus, changes in activity for these two segments must be interpreted cautiously. The variance value is lowest for the anterolateral and posterior segments. Changes in activity for these two segments can be interpreted with greater confidence.

When only one observer is available, diagnostic accuracy is improved by the use of criteria for interpretation based on an interobserver variance analysis. When feasible, thallium stress tests should be interpreted by multiple observers because errors due to observer variance can be reduced and, thus, diagnostic accuracy improved. Averaging of the multiple observer scores and interpretation of the averaged scores using the average criteria appears to be more useful than interpretation by simple consensus.

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Echocardiographic Features of Atrioventricular and Ventriculoatrial Conduction

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The potential application of diagnostic ultrasound to understanding of the hemodynamic effects of various rhythm and conduction disturbances has not been fully explored. To investigate the changes in cardiac function associated with various atrioventricular (A-V) sequencing intervals during cardiac pacing, simultaneous M mode and two dimensional echocardiographic and hemodynamic studies were performed in 23 dogs.

One to one A-V and ventriculoatrial (V-A) sequential pacing at cycle lengths of 400 and 300 ms revealed a stepwise reduction in left ventricular pressure and cardiac output as the A-V interval was changed from +100 to −100 ms. These reductions in cardiac hemodynamics were associated with decreases in left ventricular and increases in left atrial dimensions determined with echocardiography. Mitral valve excursion and the duration of valve opening remained constant over the entire range of A-V intervals. There was angiographic evidence of retrograde blood flow from the left atrium into the pulmonary venous system at an A-V interval of −50 and −100 ms, but no evidence of mitral regurgitation.

Thus, correlative echocardiographic and hemodynamic studies can suggest multiple pathophysiologic mechanisms contributing to the decrements in cardiac function observed during tachyarrhythmias with intact A-V conduction as well as those occurring consequent to A-V nodal Wenckebach cycles.

Echocardiography has revealed abnormal and occasionally characteristic ventricular wall motion patterns in association with a variety of electrocardiographic abnormalities. These electrocardiographic changes include the alterations in conduction associated with left bundle branch block,[1–3] accelerated idioventricular rhythms,[4] preexcitation syndromes[5–9] and, most consistently, with ventricular ectopic beats.[10] Furthermore, patients with various forms of preexcitation may have such well defined wall motion abnormalities that these are virtually diagnostic for the ventricular site of insertion of the bypass tract.[4,5,9] Typically, left ventricular posterior wall bypass tracts are detected more consistently than are those coursing through the interventricular septum.[8,9]

Previous investigators[10,11] have also demonstrated the potential applications of echocardiography to understanding of the effects of various rhythm and conduction disturbances on cardiac performance. DeMaria et al.[12] assessed the contribution of atrial transport to ventricular function after electroconversion of supraventricular arrhythmias by evaluating motion of the mitral valve with echocardiography. Similarly, other investigators[13,14] described the echocardiographic manifestations of mitral valve and left atrial wall motion in the presence of atrial flutter.

From previous work we have had a particular interest in the hemodynamic sequelae of both supraventricular and ventricular tachycardias, and in the hemodynamic consequences of various cardiac pacing

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TABLE I

Effects of Various Atrioventricular (A-V) Sequential Intervals on Cardiac Hemodynamics in 15 Dogs

	A-V = 100 ms		A-V = 50 ms		A-V = 0		A-V = −50 ms		A-V = −100 ms	
	CL 400	CL 300	CL 400	CL 300	CL 400	CL 300	CL 400	CL 300	CL 400	CL 300
LVP	129	121	125*	106	120*	101*	116*	93*	112*	88*
LAP	2.8	3.2	3.2	3.7	4.5*	4.8*	5.9*	6.6*	6.8*	7.8*
CO	2.83	2.63	2.26*	2.21*	1.95*	1.87*	1.91*	1.82*	1.83*	1.78*

* $p < 0.05$ (compared with value at an A-V interval of 100 ms).
CL = cycle length (ms); CO = cardiac output (liters/min); LAP = left atrial pressure (mm Hg); LVP = left ventricular systolic pressure (mm Hg).

methods.[15] Thus, the present studies were designed specifically to determine the echocardiographic correlates of changes in cardiac performance secondary to changes in atrioventricular (A-V) conduction patterns.

Methods

Experimental preparation: Twenty-three mongrel dogs weighing 13 to 20 kg were anesthetized with intravenous administration of 20 to 30 mg/kg of sodium pentobarbital (Nembutal®) and intubated. Ventilation was maintained by a Harvard respirator with use of room air. The chest was opened using a mid line incision and the pericardium was left intact. Left ventricular and aortic pressures were measured using a 7F Millar dual Mikro-Tip catheter pressure transducer (PC 771) inserted through the right femoral artery. Left atrial pressures were obtained using a 5F Millar Mikro-Tip catheter pressure transducer (PC 350) introduced through a pulmonary vein. Cardiac output measurements were made utilizing a Swan-Ganz thermodilution catheter and an Edwards 9510A cardiac output computer.

With use of 23 gauge needles, Teflon®-coated stainless steel unipolar plunge wire electrodes (0.1 mm diameter) were placed in the left atrial appendage and the myocardium of the left ventricular apex to pace the heart. The pacing stimuli were 1 ms in duration. Both atrial and ventricular pacing were applied using constant current pulses of twice diastolic threshhold. In addition, Teflon-coated, thin silver wire bipolar plunge electrodes were placed in the left atrial appendage and the left ventricular free wall in order to record the electrograms from each of these sites.

Echocardiography: M mode echocardiographic studies were obtained using a Smith-Kline Ekoline 20 interfaced with an Irex 101 Continutrace recorder. A 2.25 megahertz transducer was placed on a rigid bar that was attached to both sides of the surgical table. The methods of recording echocardiograms from the various cardiac structures were similar to those described by Kerber et al.[16] In four animals, two dimensional echocardiographic recordings were also obtained using a wide angle (90°) mechanical sector scan (Advanced Technology Laboratories, Mark III). The transducer was attached to the same bar assembly used for the M mode echocardiographic transducer.

In seven animals, an 8F catheter with multiple side holes at its tip was introduced into the left side of the heart through the left atrial appendage or retrograde through the femoral artery in order to obtain left atrial or left ventricular cineangiograms, or both, using hand injections of 5 ml of Renografin®. Contrast echocardiograms were obtained by bolus injection of saline solution directly into the left ventricle in order to determine the degree of mitral valve regurgitation.

Echocardiographic recordings of the left atrium, left ventricle, mitral and aortic valve opening were obtained during ventricular pacing at cycle lengths of 400 and 300 ms at multiple atrioventricular (A-V) intervals (+100, +50, 0, −50 and −100 ms). The echocardiographic correlate of A-V nodal Wenckebach periodicity was also evaluated in seven dogs during rapid atrial pacing at cycle lengths varying from 320 to 200 ms. Three dogs with stable, surgically induced A-V nodal heart block were studied during sequential pacing of the atria and ventricle at cycle lengths of 400 and 300 ms. The studies were repeated after the induction of atrial fibrillation

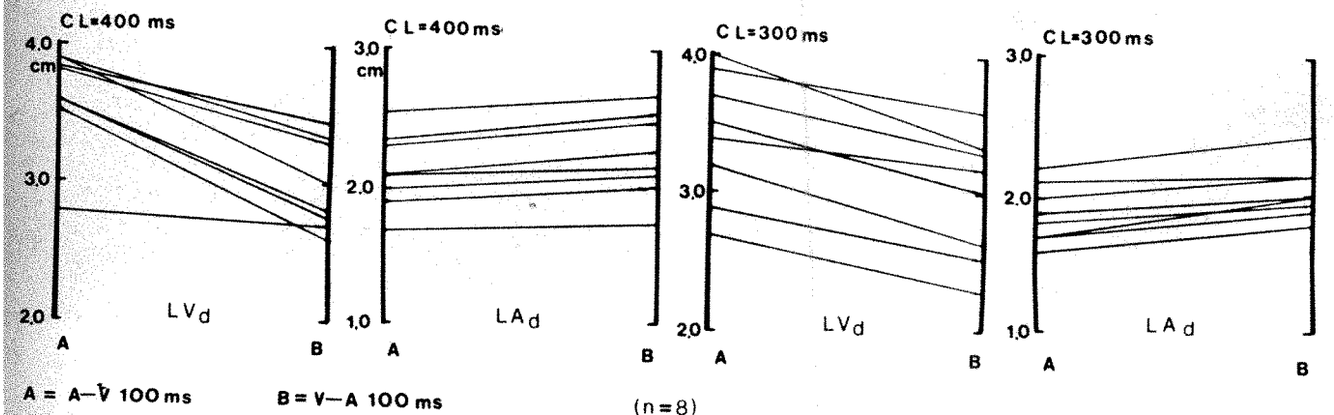


FIGURE 1. Left panels, changes in left ventricular (LVd) and left atrial dimensions (LAd) at end-diastole in centimeters are shown as the atrioventricular (A-V) pacing interval is changed from +100 ms (A) to −100 ms (B) at a cycle length (CL) of 400 ms. Note the reduction in left ventricular and increase in left atrial dimensions. **Right panels,** the same findings shown at a cycle length of 300 ms. V-A = ventriculoatrial.

and ventricular pacing at these same cycle lengths. One scalar electrocardiographic lead, left atrial, left ventricular and aortic pressures and the M mode echocardiograms were recorded simultaneously on an Irex 101 Continutrace recorder. Simultaneous electrocardiographic and pressure recordings were also obtained on a Hewlett-Packard eight channel photographic recorder (model 4578A).

Left ventricular and atrial dimensions were measured at maximal diameter. At least 10 beats were used in each record and all measurements were confirmed by two observers. Interobserver differences were within ±0.1 cm.

Results

1:1 Atrioventricular and Ventriculoatrial Pacing

• The effects of different atrioventricular (A-V) intervals on cardiac hemodynamics during A-V sequential cardiac pacing at cycle lengths of 400 and 300 ms in 15 dogs are shown in Table I. At both pacing cycle lengths there was a stepwise reduction in left ventricular pressure and cardiac output as the A-V interval was changed from +100 to +50, 0, −50 and −100 ms. These alterations in cardiac hemodynamics were associated with decreases in left ventricular and increases in left atrial dimensions determined with M mode echocardiography (Fig. 1). Figure 2 illustrates the echocardiographic alterations occurring during pacing at a constant cycle length of 400 ms when the A-V interval was changed from +100 ms (A) to −100 ms (B) (that is, ventriculoatrial (V-A) interval of 100 ms). In this representative case, left atrial dimension increased from 2.3 to 2.5 cm with a concomitant decrease in left ventricular diastolic diameter from 3.9 to 3.0 cm. At an A-V interval of −100 ms left atrial contraction occurred during the latter portion of the ventricular ejection period at a time when the A-V valves were still closed (Fig. 2B). At the shorter cycle length of 300 ms there was a similar increase in left atrial pressure and dimension and a decrease in left ventricular pressure and dimension as the A-V interval was decreased from +100 to −100 ms (Table I, Fig. 1).

Several other notable observations were made during these studies. Mitral valve excursion and the duration of valve opening remained constant over the entire range of A-V intervals studied and were independent of alterations in cardiac hemodynamics and chamber size (Fig. 3). Left atrial angiography was performed during each of these A-V sequencing intervals. Consistently, at A-V intervals of −50 and −100 ms, there was angiographic evidence of retrograde flow from the left atrium into the pulmonary venous system (Fig. 4) (that is, pulmonary venous regurgitation). Remarkably, there was no evidence of mitral regurgitation on left ventricular angiography or contrast echocardiography at any A-V interval

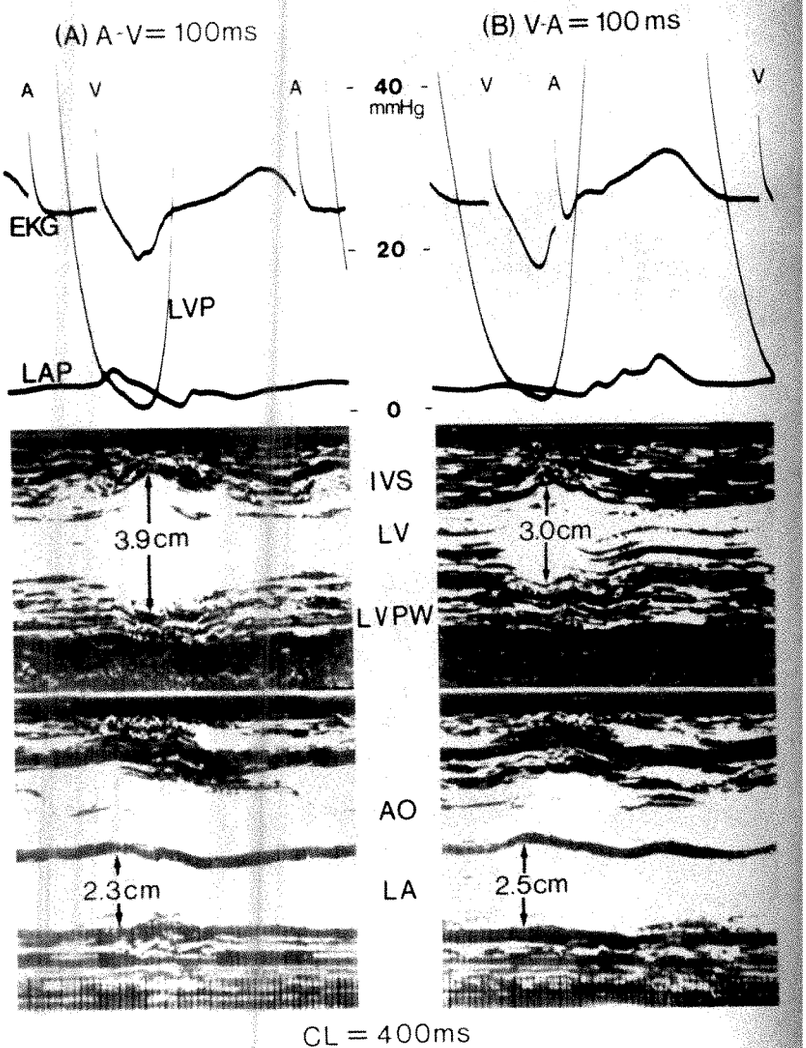


FIGURE 2. Representative study showing a marked decrease in left ventricular (LV) cavity size with a concomitant increase in left atrial (LA) dimension during abnormal atrioventricular (A-V) sequencing. **Top panel** shows the effects of an A-V interval of 100 ms at a cycle length (CL) of 400 ms in (**A**) and the effects of an A-V interval of −100 ms (V-A) in (**B**). Note the decrease in left ventricular (LV) dimension from 3.9 cm (**A**) to 3.0 cm (**B**) and an increase in left atrial (LA) dimension from 2.3 cm (**A**) to 2.5 cm (**B**). Also note the elevated left atrial pressure (LAP) during the left ventricular ejection period. A = atrial pacing spike; AO = aortic root; EKG = electrocardiogram; IVS = interventricular septum; LVP = left ventricular pressure; LVPW = left ventricular posterior wall; V = ventricular pacing spike.

during 1:1 A-V or V-A pacing at cycle lengths of 400 or 300 ms (Fig. 5, A and B). In addition, in three animals with surgically induced A-V heart block atrial fibrillation was induced by high frequency atrial pacing. Notably, in the presence of atrial fibrillation and A-V block there was also no evidence of mitral regurgitation during ventricular pacing at a fixed cycle length of 400 or 300 ms (Fig. 5C).

Rapid Atrial Pacing

Rapid atrial pacing at cycle lengths of less than 280 ms with 1:1 A-V sequencing usually resulted in both electrical and mechanical left ventricular alternans. In Figure 6 the mechanical systole after mitral valve opening and left ventricular filling was forceful and prolonged and resulted in aortic valve opening with a normal ejection period. This prolonged systole encroached on the next atrial contraction (arrow), resulting in an abortive attempt to open the mitral valve (asterisk). The next ventricular systole failed to open the aortic valve. However, this shorter systolic period engendered a more favorable A-V sequence that again enabled the mitral valve to open and facilitated left ventricular filling.

Rapid atrial pacing resulted in a Wenckebach pattern of A-V conduction (*Fig. 7*). During the prolonged pause that preceded the first conducted beat of each sequence, the lack of ventricular systole permitted an extended period of mitral valve opening and left ventricular filling. The next atrial contraction (single arrow) reopened the mitral valve and, further, actively filled the ventricle. All of these factors contributed to the subsequent enhanced and prolonged systole (360 ms) of the first conducted beat after the pause. The hemodynamic conditions preceding the second ventricular systole in the sequence (2) were much less favorable. The next

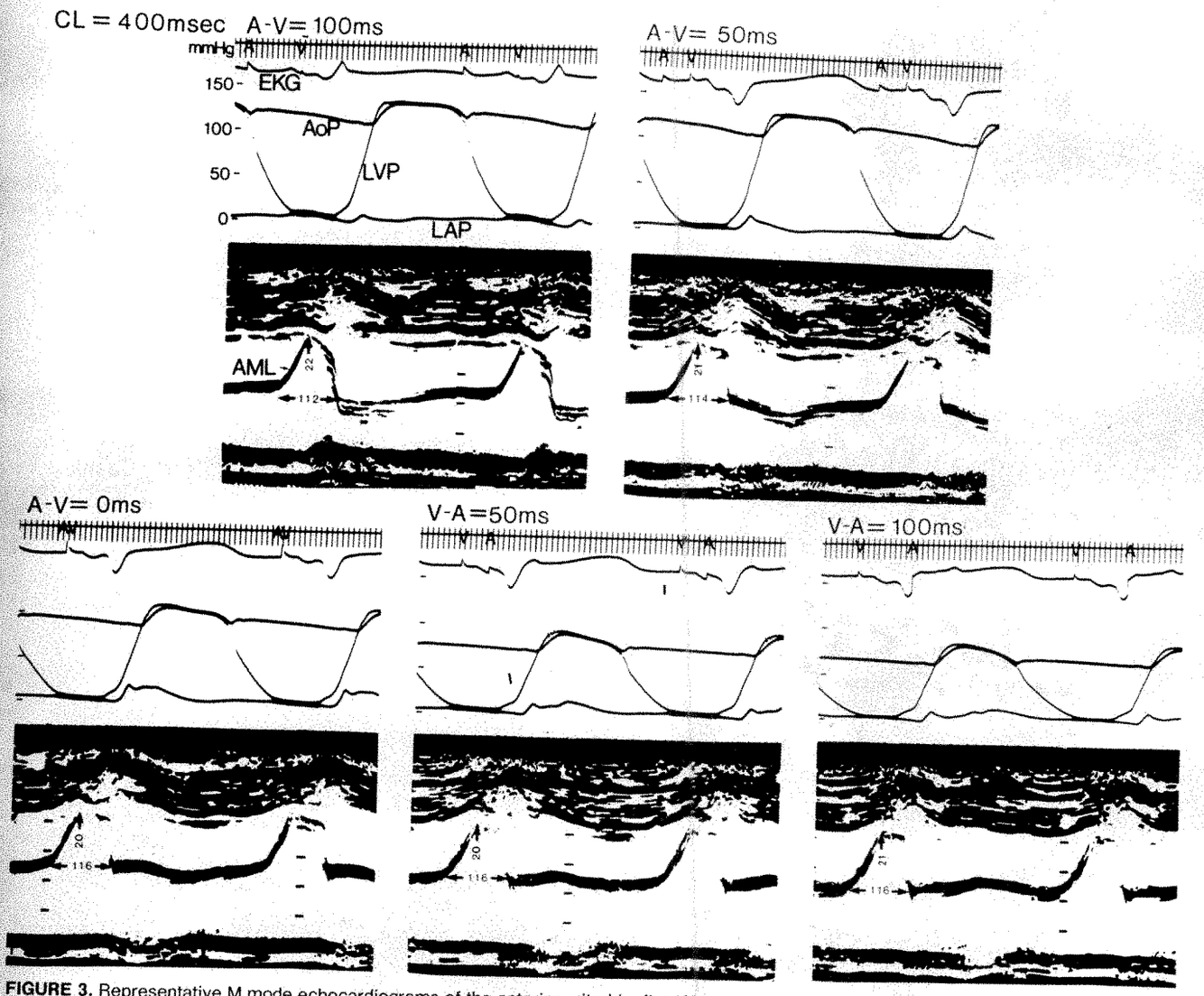


FIGURE 3. Representative M mode echocardiograms of the anterior mitral leaflet (AML) during various atrioventricular (A-V) and ventriculoatrial (V-A) intervals at a cycle length (CL) of 400 ms recorded with simultaneous pressure curves. The duration of mitral valve opening and the amplitude of excursion remain essentially constant. The numbers between two transverse arrows (←→) indicate the duration of diastolic opening of the anterior mitral leaflet in milliseconds and those under a single vertical arrow (↑) show the excursion of this leaflet in millimeters. Note the decrease in left ventricular (LVP) and aortic (AoP) pressures as the A-V interval was changed from +100 to −100 ms. A = atrial pacing spike; EKG = electrocardiogram; LAP = left atrial pressure; V = ventricular pacing spike.

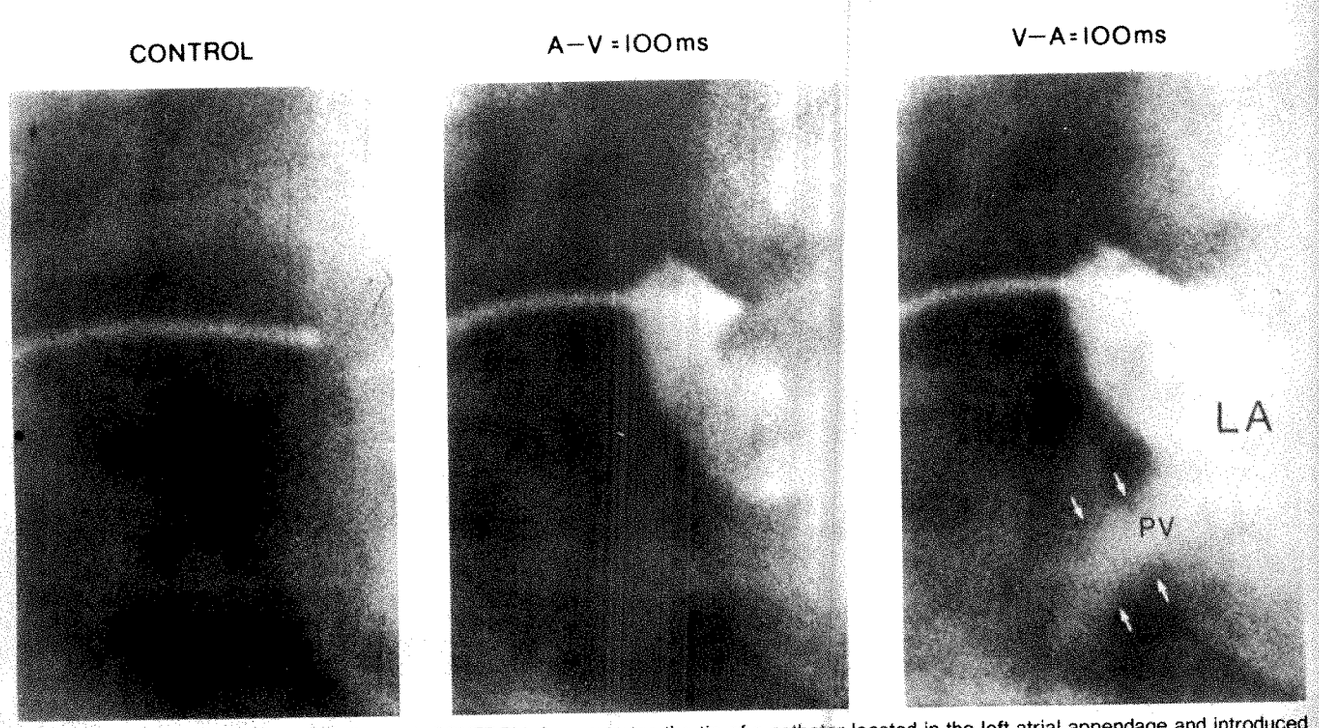


FIGURE 4. Left atrial angiograms. **Left panel** (CONTROL) demonstrates the tip of a catheter located in the left atrial appendage and introduced by way of the pulmonary vein. **Right panel** demonstrates marked regurgitation (**white arrows**) of contrast medium from the left atrium (LA) into the pulmonary vein (PV) during a ventriculoatrial (V-A) pacing interval of 100 ms at a cycle length of 400 ms. No such regurgitation is observed during an atrioventricular (A-V) interval of 100 ms at a cycle length of 400 ms (**middle panel**).

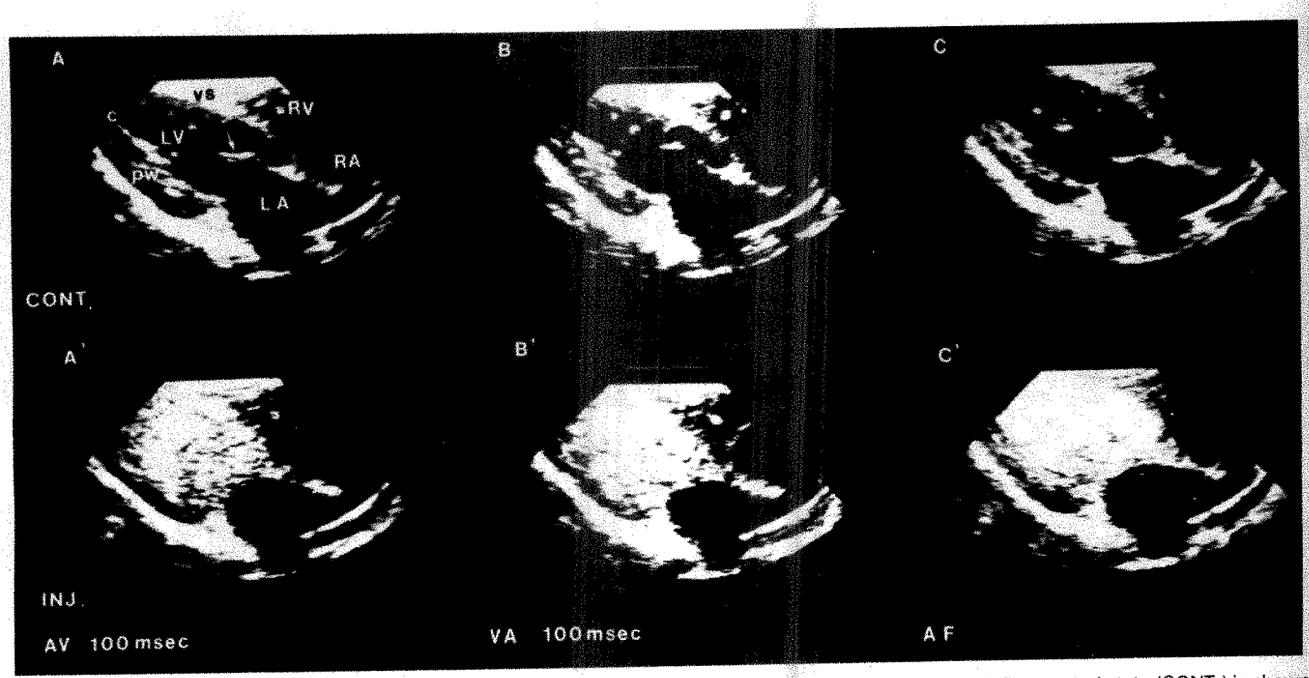


FIGURE 5. Still frames of a two dimensional echocardiographic left ventricular long axis view of a dog's heart. The control state (CONT.) is shown in the upper row (**A, B, C**) and systolic frames during saline injection (INJ) in the lower row (**A′, B′, C′**). **White arrow** in **A** indicates the anterior mitral leaflet. Changing the pacing sequence from an atrioventricular (A-V) interval of 100 ms (**A, A′**) to a ventriculoatrial (V-A) interval of 100 ms (**B, B′**) does not result in mitral regurgitation (that is, there are no saline microbubbles present in the left atrium in systole). Similarly, there is no evidence of mitral regurgitation in the presence of atrial fibrillation (A F) and A-V block with a constant ventricular rate (**C** and **C′**). LA = left atrium; LV = left ventricle; msec = milliseconds; pw = left ventricular posterior wall; RA = right atrium; RV = right ventricle; vs = interventricular septum.

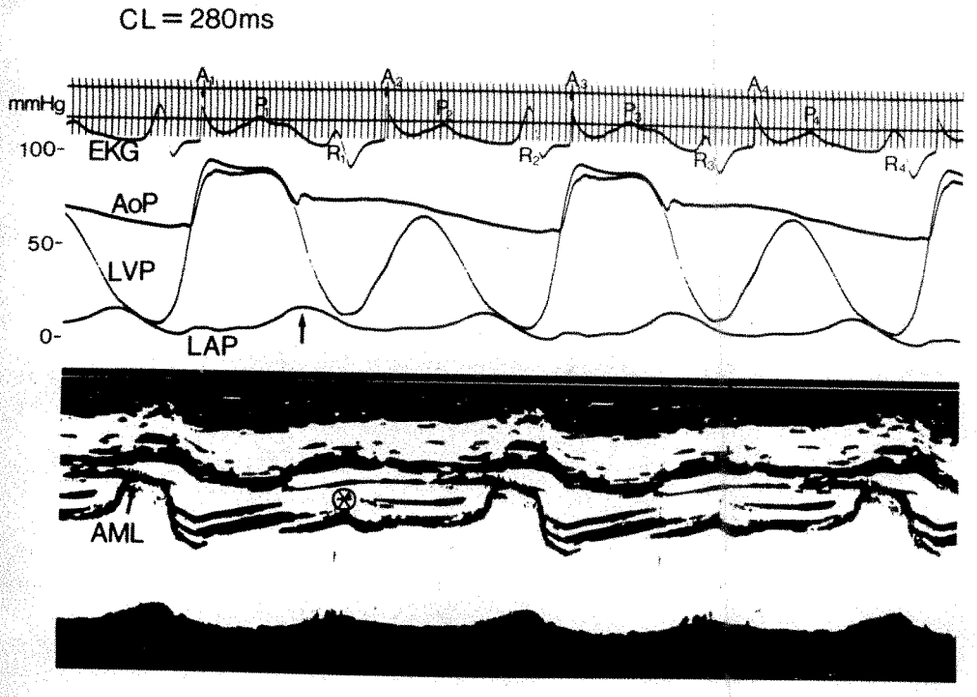


FIGURE 6. Rapid atrial pacing at a cycle length (CL) of 280 ms in this representative study shows the induction of left ventricular mechanical and electrical alternans. Pressure relations among the aorta (AoP), left ventricle (LVP) and left atrium (LAP) are shown in the **upper panel** and the echogram of the anterior mitral leaflet (AML) is shown in the **lower panel.** Note that the encroachment of the prolonged mechanical systole after the anterior mitral leaflet opening on the next atrial contraction (**black arrow** on the left atrial pressure curve) resulted in an abortive opening of the anterior mitral leaflet (**circled asterisk**). A = atrial pacing spike; EKG = electrocardiogram; P = P wave; R = QRS complex.

atrial contraction (double arrows) could not contribute to left ventricular filling because it occurred during ventricular systole. In addition, passive left ventricular filling as evidenced by mitral valve opening was shortened by encroachment of the next ventricular systole on the previous one, as dictated by the progressive shortening of the R-R intervals during typical Wenckebach sequences. The combination of these hemodynamic events resulted in a less powerful ventricular systole that failed to open the aortic valve.

The hemodynamic conditions became even more complex when rapid atrial pacing caused a combination of a 3:2 Wenckebach periodicity and an absolute 2:1 left ventricular and atrial alternans (Fig. 8). Because only every other electrical systole (R_1, R_4, R_7) resulted in a mechanical response, the passive mitral valve opening time was unusually prolonged. Atrial contraction after A_6 enhanced opening of the mitral valve (asterisk). Of note, because of the superimposed atrial alternans, effective atrial contractions occurred only

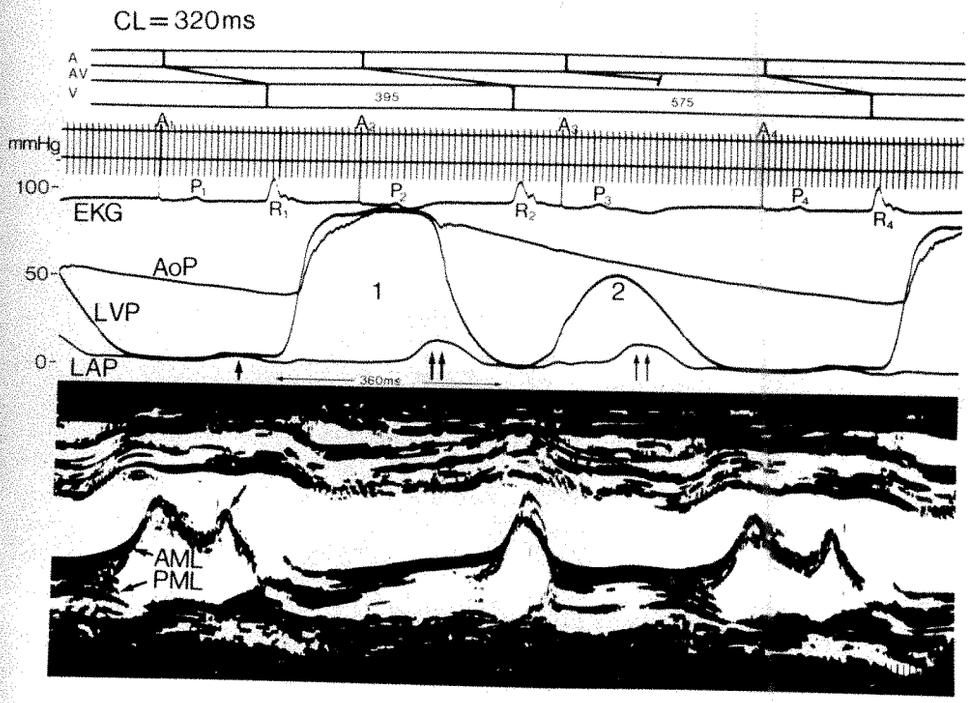


FIGURE 7. Rapid atrial pacing at a cycle length (CL) of 320 ms in a representative dog resulted in 3:2 Wenckebach periodicity. The ladder diagram depicts the conduction pattern. Note that the prolonged period of the mitral valve opening (**single arrow** on the echogram of the anterior mitral leaflet [AML]) after a dropped beat results in a forceful and prolonged (360 ms) mechanical systole (1), and that the passive left ventricular filling of this cycle is shortened because of the encroachment of the next ventricular systole (2) on the previous one (1). Also note that the atrial contraction varies depending on whether it occurs during the ventricular ejection period (**single** and **double arrows** on the left atrial pressure [LAP] tracer). A = atrial pacing spike; AoP = aortic pressure; EKG = electrocardiogram; LAP = left atrial pressure; P = P wave; PML = posterior mitral leaflet; R = QRS complex.

after each effective second ventricular systole (asterisk). Note the absence of the expected increase in atrial pressure (double arrows) during the ventricular ejection period and the closed mitral valve caused by the atrial alternans. Thus, although atrial contractions occurred at the same position in diastole during different cycles (arrow) they failed to open the mitral valve consistently.

Discussion

Alterations in cardiac function associated with various cardiac arrhythmias have previously been studied but have routinely been limited to measurements of traditional hemodynamic variables.[15,17] Using conventional methods, several investigators[15,17,18] have suggested that the hemodynamic consequences of various changes in the sequence of A-V activation and in the degree of irregularity of successive cardiac cycles may also result from secondary vasomotor and neurohumoral mechanisms. It has long been recognized[19] that the so-called atrial booster pump action present during normal A-V sequencing results in an increase in ventricular volume at end-diastole so that an approximately 10 to 20 percent larger cardiac output occurs than in the presence of A-V block. Furthermore, P wave synchronous pacing in complete A-V heart block results in a cardiac output approximately 10 to 15 percent greater than that with ventricular pacing at the same ventricular rates.[20]

Hemodynamic and chamber size alterations during A-V and V-A pacing: In a previous study,[21] we demonstrated that M mode echocardiography was useful in identifying the changes in cardiac function that occur in the presence of various patterns of A-V and V-A conduction. In this study, changes in cardiac hemodynamics and cardiac chamber sizes were evaluated by scanning the A-V interval from +100 to −100 ms in the presence of A-V and V-A sequential pacing. We observed progressive decreases in systolic blood pressure, cardiac output and left ventricular size concomitant with increases in left atrial size. As atrial systole moved into the period of mechanical ventricular systole, the contraction of the left atrium against the closed mitral valve resulted in marked regurgitation of blood into the pulmonary venous system (Fig. 4). Hence, it would appear that, in addition to the direct loss of the atrial contribution to ventricular filling, there was also a secondary and significant loss resulting from retrograde propulsion of blood during V-A conduction. Thus, even "stable" sustained ventricular rhythms with intact V-A conduction can result in serious hemodynamic consequences. In contrast, ventricular pacing or tachycardia in the presence of A-V block appeared hemodynamically relatively less deleterious because there was only a random rather than regular and inadvertent association of atrial and ventricular systole.[15] Similarly, the occurrence of atrial fibrillation in association with rapid ventricular rhythms was also apparently less deleterious hemodynamically than the presence of intact 1:1 rapid retrograde V-A conduction.[15]

Mitral valve function: Remarkably, the alterations in cardiac hemodynamics and changes in chamber dimensions during rapid 1:1 A-V pacing at various sequencing intervals were not reflected in the echocardiographic features of mitral valve function (Fig. 3). However, the variations in ventricular cycle lengths that

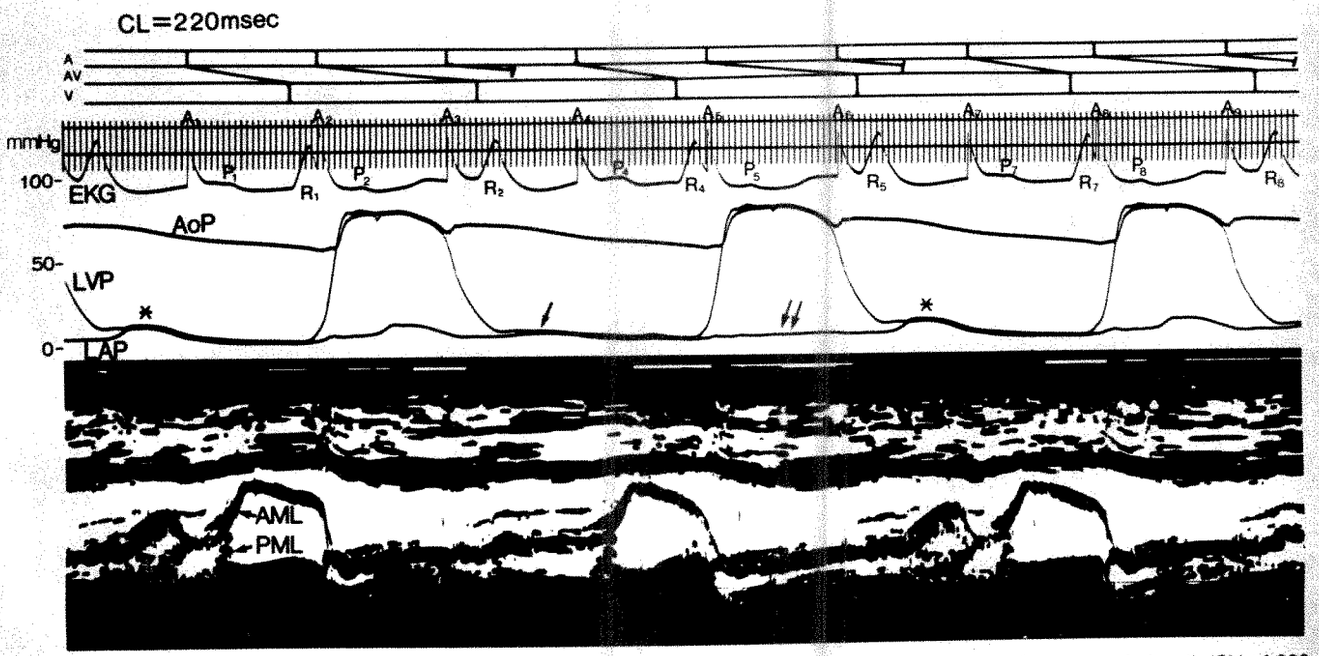


FIGURE 8. Wenckebach periodicity (3:2) with left ventricular and atrial alternans observed in a representative dog at a cycle length (CL) of 220 ms. The ladder diagram relates atrial pacing stimuli (A) to atrial activation (P) and ventricular activation (R). Aortic (AoP), left ventricular (LVP) and left atrial (LAP) pressures show complex patterns of left atrial and left ventricular alternans. Note the difference between the high (**asterisk**) and low (**arrows**) left atrial pressures. AML = anterior mitral leaflet; EKG = electrocardiogram; PML = posterior mitral leaflet.

occurred in association with progressive P-R interval prolongation during A-V nodal Wenckebach periods did affect mitral valve motion, and often obliterated the usual presystolic reversal of the A-V pressure gradient that normally places the A-V valve leaflets in a position to close early at the onset of ventricular systole. Hence, A-V valve regurgitation was observed during rapid atrial pacing causing Wenckebach periodicity and irregular R-R intervals (Fig. 9). Mitral regurgitation was never observed during sustained periods of V-A activation with constant P-R or R-P intervals as long as the R-R intervals remained constant (Fig. 5, A and B).[22] This was true even in the presence of atrial fibrillation in the dogs with heart block when the R-R intervals were kept constant (Fig. 5C).

Echocardiographic changes during Wenckebach conduction: D'Cruz et al.[23] observed that during 3:2 A-V Wenckebach conduction patterns, ventricular beats exhibited alternating long and short periods of systolic opening of the pulmonary and aortic valves and alternately large and small left ventricular stroke volumes. Left ventricular stroke volume in these cases appeared to be directly proportional to the preceding end-diastolic volume. Other investigators[24] observed alternating failure of mechanical responses to electrical depolarizations during A-V Wenckebach periods in addition to those ventricular contractions lost secondary to periodic A-V block, but the precise mechanism of this phenomenon has eluded clear definition. The echocardiographic observations made in our study have revealed an important mechanism contributing to the compromised hemodynamics during typical A-V Wenckebach periods in which R-R intervals shorten successively. At critical P-R and R-R intervals there is increasing encroachment of a subsequent atrial systole into the left ventricular ejection period of the previous systole. This successively shortens the duration of the opening of the mitral valve, abolishes active atrial transport and thereby reduces left ventricular filling. Other Wenckebach patterns might further compromise cardiac hemodynamics. However, the longer pause that follows the dropped beat does enable adequate mitral valve opening and left ventricular filling and thereby facilitates an effective subsequent beat (Fig. 7).

Clinical implications: As shown in the present study, echocardiography can provide considerable insight into the mechanisms responsible for the marked hemodynamic derangements that result from various patterns of A-V conduction. Such deleterious hemodynamic consequences could not be anticipated from

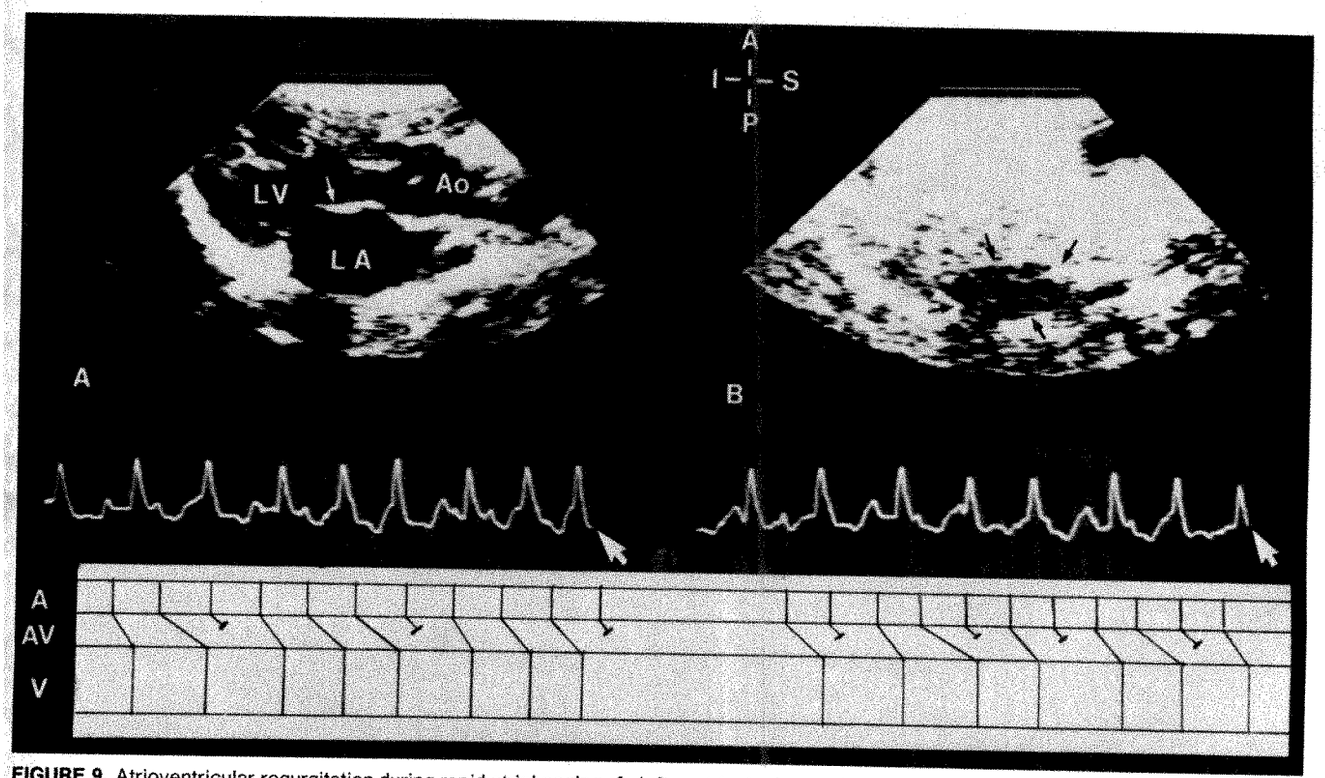


FIGURE 9. Atrioventricular regurgitation during rapid atrial pacing. **A,** left ventricular long axis two dimensional echocardiographic view of a representative dog heart during rapid atrial pacing causing Wenckebach periodicity. Ao = aorta; LA = left atrium; LV = left ventricle. The anterior mitral leaflet is marked by a **white arrow. B,** a still frame during systole of the same dog during saline injection into the left ventricle. Regurgitation of contrast medium into the left atrium is indicated by the **black arrows.** The **arrow** to the **right** of the electrocardiogram indicates the precise timing of the stop-frame echocardiogram. The lower part of the figure shows the electrocardiogram and corresponding ladder diagram (A = atrial; A-V = atrioventricular; V = ventricular conduction). **At top of figure,** A = anterior; I = inferior; P = posterior; S = superior.

analyses limited to the electrocardiogram. Echocardiography can be especially useful in understanding the effects of complex abnormalities such as those resulting from the superimposition of mechanical (for example, alternans) and electrical (for example, Wenckebach periodicity) phenomena during supraventricular arrhythmias. In addition, these studies provide further experimental evidence emphasizing the potential clinical benefits of those cardiac pacing methods that provide optimal A-V sequencing intervals.

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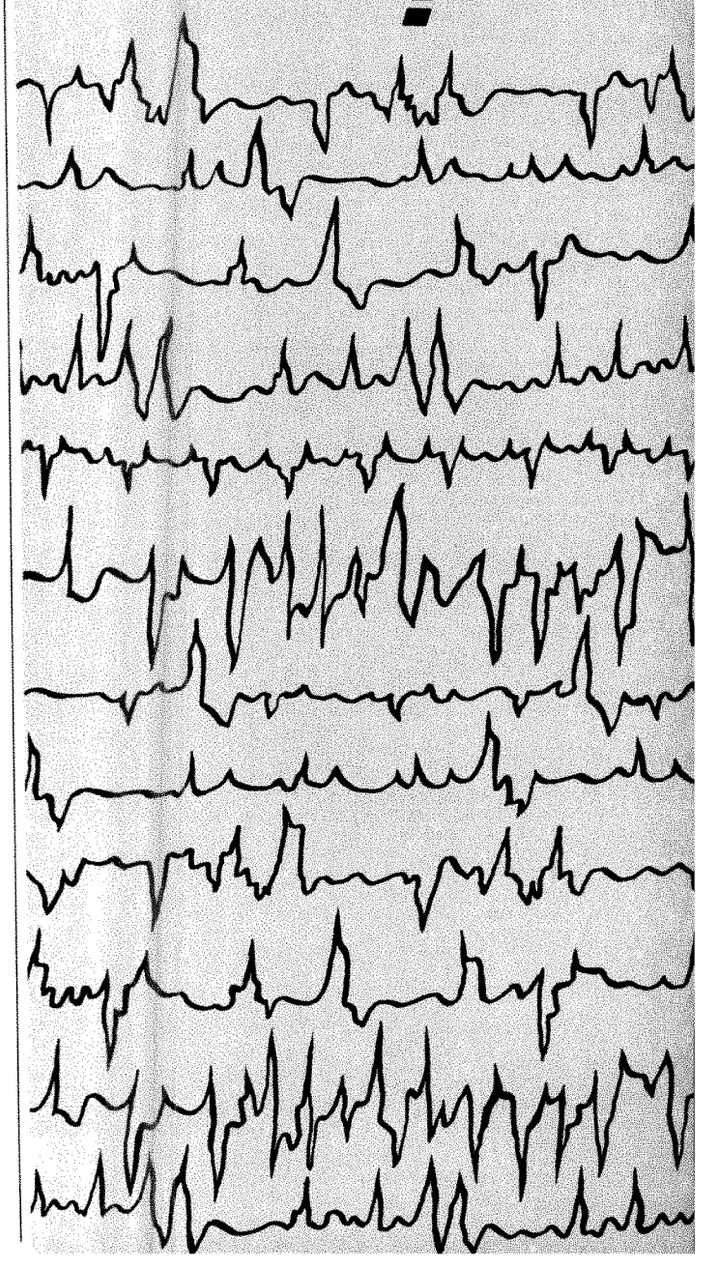
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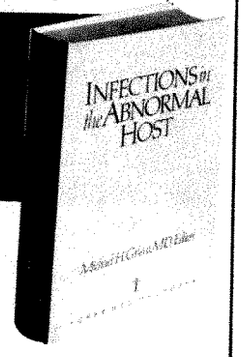
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Norpace®
(disopyramide phosphate)

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows. ***Indications:*** *For suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion). Norpace is equally effective in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.* ***Contraindications:*** *Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.* ***Warnings:*** ***Norpace may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and discontinuation of Norpace considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. The concomitant use of Norpace with other Type 1 antiarrhythmic agents should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.*** ***Precautions:*** *Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood* ***Norpace has been reported to stimulate contractions of the pregnant uterus.*** *Use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown. Safety and effectiveness of Norpace in children have not been established.* ***Adverse Reactions:*** *Dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention, urinary frequency and urgency, impotence, nausea, pain/bloating/gas, anorexia, diarrhea, vomiting, nervousness, dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains, hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain, generalized rash/dermatoses, itching, hypokalemia, elevated cholesterol/triglycerides, depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit, and hypoglycemia. Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported.* ***Dosage and Administration:*** *Dosage must be individualized on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually with close monitoring.* ***See current complete prescribing information for dosage recommendations. How Supplied:*** *Capsules containing 100 mg or 150 mg of disopyramide base.*

SEARLE *Searle Laboratories*
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

The answer is...

Norpace® *in specific ventricular arrhythmias**

(disopyramide phosphate)



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Proved with Holter recordings in double-blind clinical trials

More compatible with digoxin

Norpace, unlike quinidine, does not cause elevation of serum digoxin levels[2]

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One fourth the dropout rate vs quinidine in double-blind clinical trials

Outstanding patient acceptance

- *Easily individualized dosing*
- *Usually well tolerated – even during long-term administration*

As with any antiarrhythmic drug, serious adverse reactions may occur in patients taking Norpace. Please see the facing page for a brief summary of prescribing information.

References: *1. Data on file, Searle Pharmaceuticals Inc. 2. Leahey, E.B., Jr., and others: The Effect of Quinidine and Other Oral Antiarrhythmic Drugs on Serum Digoxin: A Prospective Study, Ann. Intern. Med. 92:605-608 (May) 1980.*

***Indicated for premature ventricular contractions (PVCs)... unifocal, multifocal, or paired PVCs... episodes of ventricular tachycardia.**

SEARLE

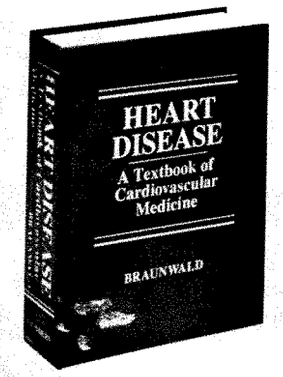
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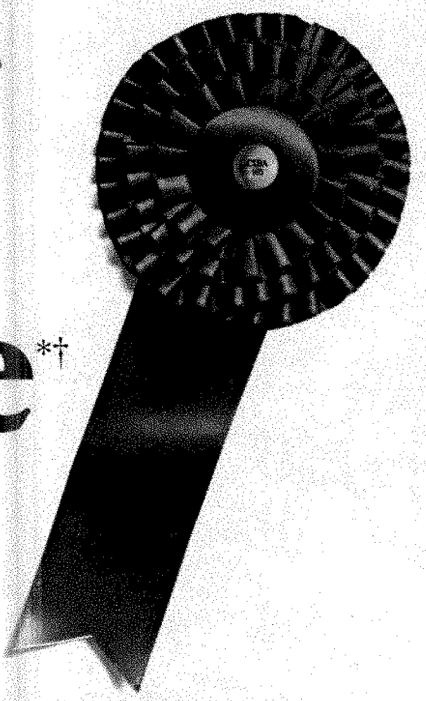
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Over 15 years of worldwide clinical experience*†



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†Slow-release potassium chloride tablets should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid K preparations because of reports of GI ulceration and bleeding with slow-release KCl tablets (total number of GI lesions in both foreign countries and the United States remains less than one per 100,000 patient-years). The incidence of lesions with enteric-coated KCl tablets is 40-50 per 100,000 patient-years.

Please turn page for brief prescribing information.

Experience makes a difference.

Slow-K®

CIBA 165

potassium chloride slow-release tablets 8 mEq

CIBA

potassium chloride slow-release tablets

DESCRIPTION

Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS

BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS

In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS

Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS

Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE

Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

667112

C78-23 (4/78)

Consult complete product literature before prescribing.

128-2715-A

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

C I B A

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have hac elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

***Dosage:* Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

***How Supplied:* 0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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The anxious heart. Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.



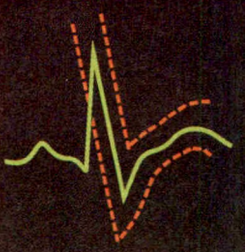
*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Ativan® (lorazepam) for Anxiety

No other arrhythmia detection system gives you all t

1



Dramatically reduced false alarms

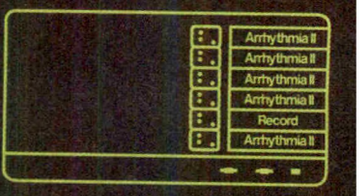
We start with template matching—the preferred method—to discriminate between the patient's dominant beat and ectopics. But only Arrhythmia II adds two unique features to screen out artifact, ensuring that only qualified ectopic activity triggers alarms or is included in trends: (1) each abnormal beat must appear four times before it's accepted as a "true" ectopic class, and (2) our "over-range" circuitry suspends ECG processing for a minimum of five seconds when it detects excessive noise.

MEMORY BANK OF CLASSES / NUMBER OF OCCURRENCES

		1	2	3	4	5	6	7 →
C-0	NORMAL	*	*	*	*	*	*	* *
C-1		•	•	•	•	*	*	
C-2		•	•					
C-3		•						
C-4		•	•	•	•	*		
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C-9								
C-10								
C-11								
C-12								
C-13	COUPLET							
C-14	DROPPED BEAT							
C-15	PACED							

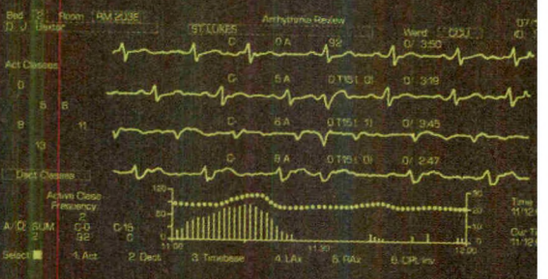
4-MATCH CRITERIA

2

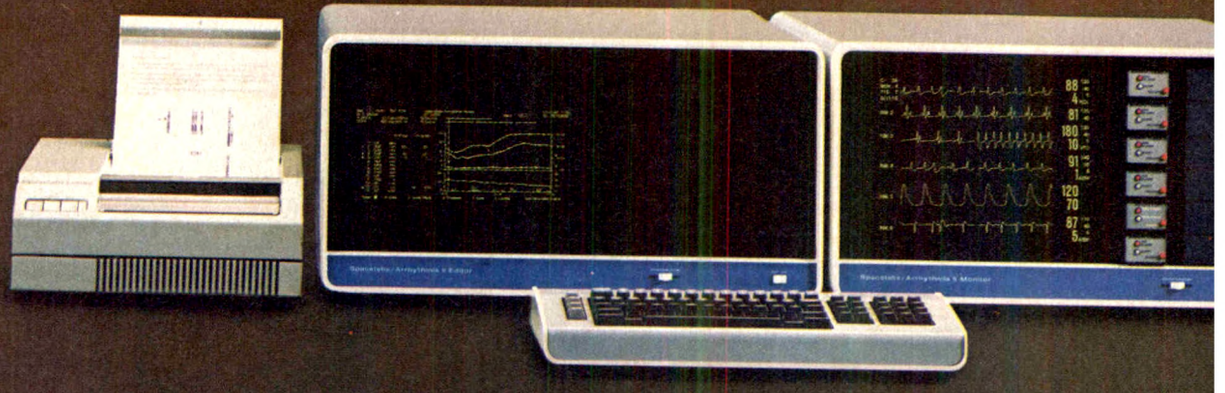


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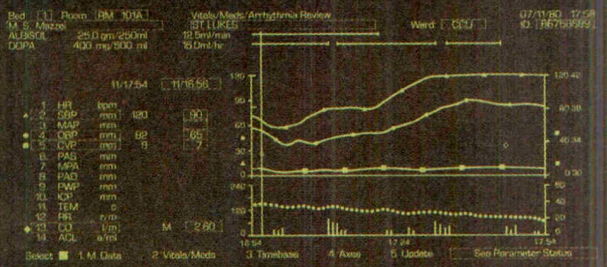
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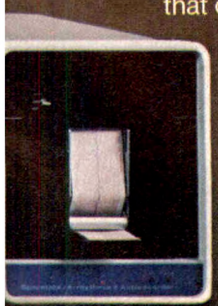
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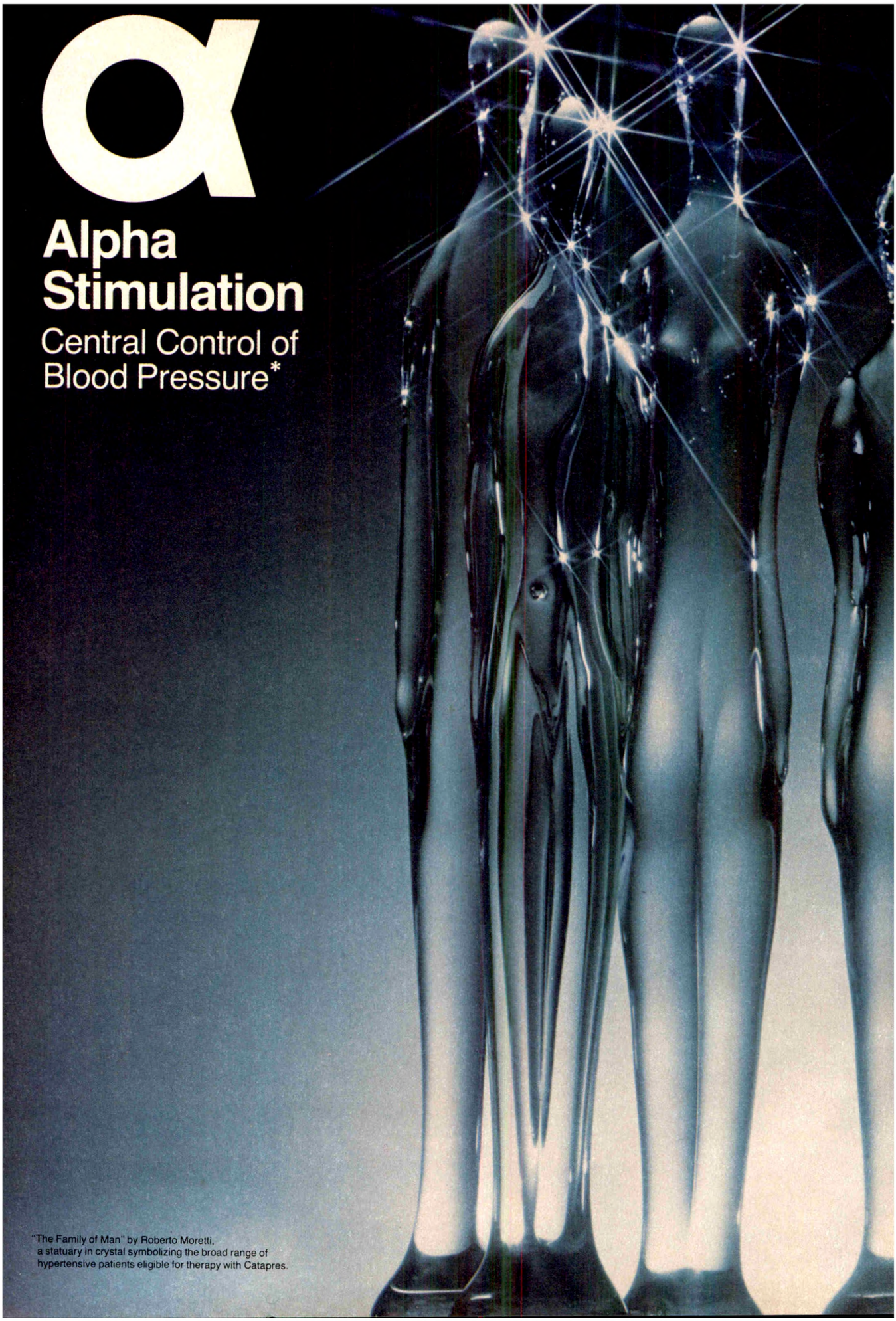
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Ventricular hypertrophy	Hepatic disease
Hyperglycemia	Hyperuricemia
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Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

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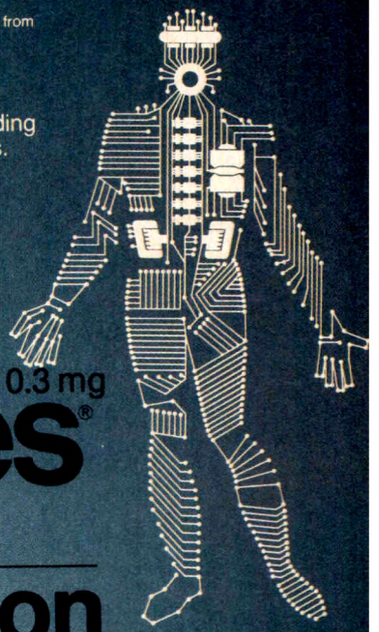
The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

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Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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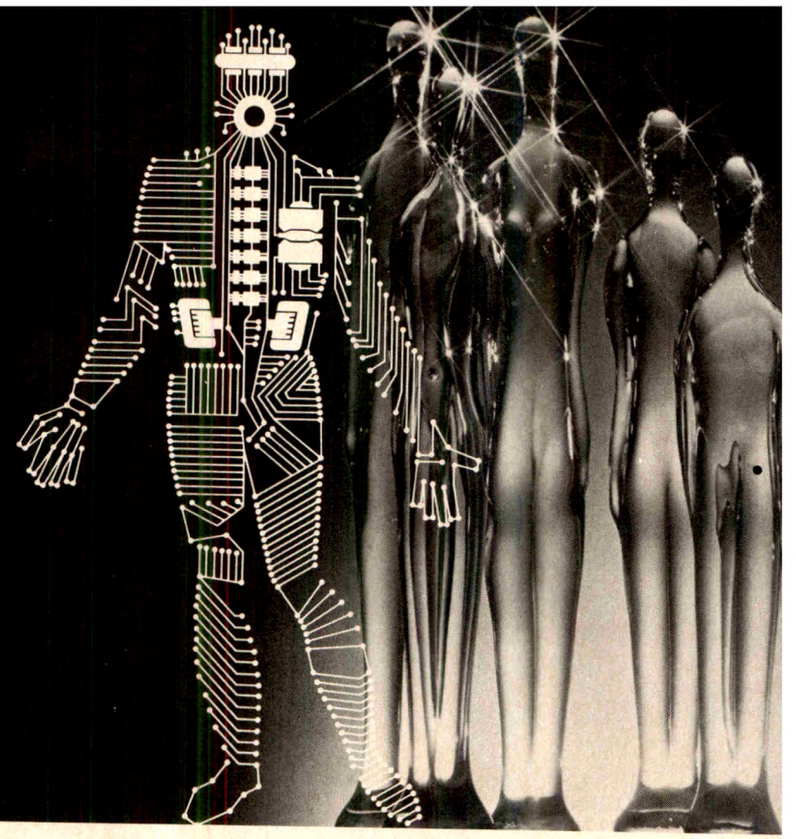


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The usual starting dose of Catapres is 0.1 mg at brea fast and 0.1 mg at bedtime. Some patients may bene from a starting dose of 0.1 mg at bedtime.

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Maximum daily dose—2.4 mg
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Tablets of 0.1, 0.2, 0.3 mg

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mon longer.

Adverse Reactions: The most common reactions are dry mouth, drowsines sedation. Constipation, dizziness, headache, and fatigue have been rep Generally these effects tend to diminish with continued therapy. The follo reactions have been associated with the drug, some of them rarely. (In instances an exact causal relationship has not been established.) These inc Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalit liver function tests; one report of possible drug-induced hepatitis without ic and hyperbilirubinemia in a patient receiving clonidine hydrochloride, thalidone and papaverine hydrochloride. Weight gain, transient elevation of glucose, or serum creatine phosphokinase: congestive heart failure, Rayn phenomenon; vivid dreams or nightmares, insomnia, other behavioral cha nervousness, restlessness, anxiety and mental depression. Also rash, gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not assoc with a rash, impotence, urinary retention, increased sensitivity to alcohol, dry itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecom weakly positive Coombs' test, asymptomatic electrocardiographic abnorma manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished o sent reflexes and vomiting followed the accidental ingestion of Catapres (clon hydrochloride) by several children from 19 months to 5 years of age. Ga lavage and administration of an analeptic and vasopressor led to complet covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-mi intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) dosage.

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Long-Term Evaluation (12 to 22 Years) of Open Heart Surgery for Tetralogy of Fallot

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Four hundred seventy-five patients underwent repair of tetralogy of Fallot from 1955 to 1964; 396 of these were hospital survivors and were followed up for 12 to 22 years. An excellent late clinical result was maintained by 87 percent of the 396 hospital survivors. A less than excellent result in the remaining 13 percent of hospital survivors was caused by late mortality in 7 percent (sudden death in 3 percent, death due to cardiac causes in 2 percent and death due to noncardiac causes in 2 percent), required reoperation in 4 percent (mainly because of residual ventricular septal defect) and development of symptoms in 2 percent.

Postoperative cardiomegaly (cardiothoracic ratio greater than 0.55) was observed in 60 (25 percent) of 246 patients who had a follow-up chest roentgenogram, and was more common among those who died late or remained symptomatic. Among the few patients with inadequate surgical relief of right ventricular hypertension who did not have transanular patch repair, the hypertension did not tend to decrease progressively, whereas it did decrease in patients who had patch repair. No late sudden deaths were encountered in 20 patients shown to have postoperative right bundle branch block plus left axis deviation (bifascicular block pattern). Pulmonary valve incompetence appeared to have relatively little harmful influence on the late result, causing cardiac disability in 1 percent of the patients and appeared to be the main contributing factor of postoperative cardiomegaly in 13 (5 percent) of the 246 patients who had a follow-up chest roentgenogram. Most late deaths and complications appeared within 2 years of operation, and accelerating deterioration in late results did not occur as the follow-up extended beyond 2 decades.

Intracardiac repair of tetralogy of Fallot has been available for more than 2 decades.[1] During the 1st decade, surgical techniques evolved rapidly—especially with respect to the closure of ventricular septal defect, the outflow tract reconstruction, and the avoidance of surgical damage to the electrical conducting system.[2] After the relative standardization of the surgical technique, interest has been directed to the late results of the operation, especially to the clinical and hemodynamic results and the factors by which late morbidity and mortality might be affected. Among these factors, the most controversial ones are the timing of operation, the indication for outflow patch reconstruction, the identification of patients at risk for late sudden death and the long-term cardiac tolerance of residual significant pulmonary valve incompetence.[3] The present study pursues these controversial factors by analyzing the long-term follow-up of a large series of patients, the earliest operated on for tetralogy of Fallot at the Mayo Clinic.

Methods

Selection of patients: Our definition of tetralogy of Fallot was based on the following qualifying criteria: (1) a large or nonrestrictive ventricular septal defect permitting equalization of pressures between the right and left ventricles, and (2) right ventricular outflow obstruction sufficient to maintain pulmonary arterial systolic pressure no greater than 35 mm Hg; patients whose pulmonary pressure was higher than 35 mm Hg secondary to a previously constructed sys-

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TABLE I

Age Distribution of Patients

Age (yr)	Patients	
	n	%
0–1	6	1
2–4	78	16
5–9	184	39
10–19	147	31
20–54	60	13
Total	475	100

temic-pulmonary shunt were included. Luminal continuity between the right ventricle and bilateral pulmonary artery was required; thus, patients were excluded who had congenital or acquired pulmonary atresia or absence of one pulmonary artery. In addition, patients with other major congenital cardiac anomalies were also excluded. Follow-up information was obtained from examinations at the Mayo Clinic, or from responses to letters or telephone calls to the patients or relatives and to the referring physicians; from an original total of 496 patients, the 21 patients for whom complete follow-up data were not obtained (all residing outside the United States) were excluded from the study.

Study patients: Thus, the study group comprised 475 patients, 298 male and 177 female, who underwent intracardiac repair of tetralogy of Fallot at the Mayo Clinic between January 1955 and December 1964. In all 475 patients, the complete follow-up information as defined was obtained in 1976; therefore, all patients were followed up for a minimum of 12 years (or until death, if it occurred in less than 12 years or early postoperatively) and for a maximum of 22 years. The age distribution of the 475 patients in the study group is listed in Table I. Eighty-four patients had primary intracardiac repair within the first 4 years of life and 60 patients between the ages of 20 and 55 years. Before intracardiac repair, 155 patients (33 percent) had had a previous palliative operation: 121 patients had a Blalock-Taussig anastomosis,[4] 27 a Potts-Smith-Gibson anastomosis[5] and 7 a Brock valvulotomy or infundibulectomy, or both.[6] As a measure of residual outflow tract stenosis, intraoperative right ventricular to left ventricular peak pressure ratio was measured after cardiac repair in 438 patients (92 percent).

Postoperative studies: A postoperative cardiac catheterization study was performed in only a selected group of 83 patients; the study was performed 2 weeks postoperatively in about 25 percent of the patients, between 1 and 9 years postoperatively in about 50 percent and between 10 and 21 years postoperatively in the remaining 25 percent. In almost 33 percent of these patients, the catheterization study was performed on a routine follow-up basis; in the remaining 67 percent, it was performed to assess the possibility of residual ventricular septal defect or right-sided outflow obstruction. A total of 246 hospital survivors had follow-up chest roentgenograms that were available to us and were obtained at a median postoperative time of 6 years (range 1 to 22). All hospital survivors had at least two postoperative electrocardiograms that were reviewed by us: one obtained before dismissal from the hospital, and one obtained late postoperatively at a median time of 3 years. The possibility of residual pulmonary valve incompetence was clinically assessed in all hospital survivors before dismissal from the hospital and late postoperatively, either at the follow-up visits at the Mayo Clinic (about half of the patients) or by the local cardiologist. Residual pulmonary valve incompetence was judged significant when there was a loud (grade 2-3/6), low pitched early diastolic decrescendo murmur at the left sternal border, which usually was associated with a thrill.

Results

Symptomatic Results

The overall results of this long-term follow-up study of 475 patients operated on for tetralogy of Fallot are summarized in Table II. An excellent symptomatic result, as judged by the patients' being asymptomatic and having no limitations of usual activities, was obtained in 73 percent of the total group and in 87 percent of the hospital survivors. Thus far, of 150 female patients with an excellent symptomatic result, 27 have had an uneventful pregnancy and 1 had a spontaneous abortion.

A fair symptomatic result, as indicated by mild to moderate physical limitation (see causes in Table II), was obtained in 2 percent of patients. Nineteen patients (4 percent of the total group and 5 percent of hospital survivors) underwent reoperation; of these 19 patients, 4 died at the time of reoperation (21 percent mortality rate) and 1 died late postoperatively. The hospital mortality rate in those early years of open heart surgery was 16 percent. The late mortality rate was 6 percent.

The actuarial curves of survival and survival with an excellent result are shown in Figure 1. These demonstrate that most late problems appear within 2 years of operation, but that thereafter the slope of the line is nearly horizontal and comparable with that of the

TABLE II

Overall Operative Results

Result	Total		1955–1959		1960–1964	
	n	%	n	%	n	%
Excellent*	345	73	100	57	245	83
Fair†	10	2	8	4	2	1
Reoperation (alive)	14	3	8	4	6	2
Hospital mortality	79	16	46	26	33	11
Late mortality‡	27	6	17	9	10	3
Total	475	100	179	100	296	100

* On selected catheterization, 11 patients have ventricular septal defect with less than 1.5:1 shunt; 5 patients have persistent outflow gradient with a right to left ventricular peak pressure ratio higher than 0.65. † Three patients probably have primary myocardial dysfunction as judged from the persistent cardiomegaly that was already present preoperatively (no prior anastomotic operation) and lack of postoperative evidence of pulmonary valve incompetence; two patients have significant pulmonary valve incompetence; four have a permanent pacemaker and one patient has recurrent supraventricular tachycardia. ‡ Four patients died at time of reoperation and one patient died 5 years after reoperation.

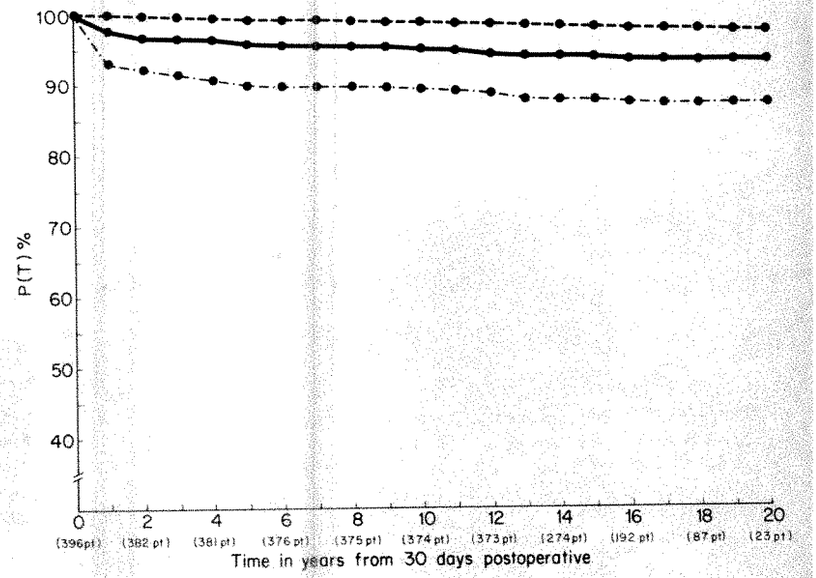


FIGURE 1. Probability of deterioration [P(T)] in operative survivors plotted against time in years. Time of deterioration is defined as postoperative year in which late death occurred (**middle curve**) or in which death, reoperation or symptoms occurred (**bottom curve**). The **top curve** represents the control expected survivorship on the basis of age and sex distribution, under the death rates of the Minnesota 1970 white population life table. The number of patients (pt) seen at each follow-up interval is denoted within parentheses.

control age- and sex-matched general population. Late mortality and reoperation were the two major reasons for the decrease in excellent results during the first 2 postoperative years.

Mortality and Reoperation

Contributing factors and causes of early mortality (Table II, Fig. 2): Improvement in surgical results occurred through the years of this experience. Hospital or early mortality after total correction was importantly influenced by the age of the patients at the time of operation (Fig. 3); thus, the hospital mortality in patients operated on before age 5 years was significantly greater than that in older patients ($p < 0.01$). Intraoperatively, the right to left ventricular pressure ratio (RV/LV) after repair was significantly higher for the group that died in the early postoperative period (mean 0.638 versus 0.503; $p < 0.001$). The Armelage test for linear trend[7] in the individual patient revealed that early operative mortality was proportionally related to an RV/LV ratio of 0.65 or greater and was not influenced by a ratio of less than 0.65 (Fig. 4). In that early experience, there was evidence of a higher early mortality rate among the patients who had a transanular patch for the relief of outflow obstruction ($p < 0.01$) (Table III). This finding could be partly related to: (1) the younger age of these patients (under age 5 years) at the time of operation ($p < 0.05$), and (2) a higher intraoperative RV/LV pressure ratio (0.65 or greater) or insufficient relief of pulmonary stenosis after the repair ($p < 0.05$). The presence and type of prior palliative anastomotic operation were not associated with early death (Fig. 5). The specific causes of early mortality are expressed in Table IV.

Contributing factors and causes of late mortality: Late mortality was not influenced by the age of the patient at the time of operation (Fig. 3), by the intra-

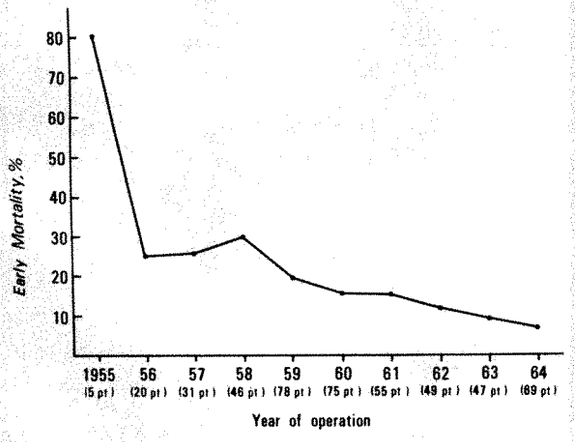


FIGURE 2. Hospital or early mortality rates (death within 30 days of operation) in 475 patients subjected to intracardiac repair for tetralogy of Fallot between 1955 and 1964, with a long-term follow-up of 12 to 22 years. Observe the improvement in surgical results through the years. The number of patients (pt) operated on each year is denoted within parentheses.

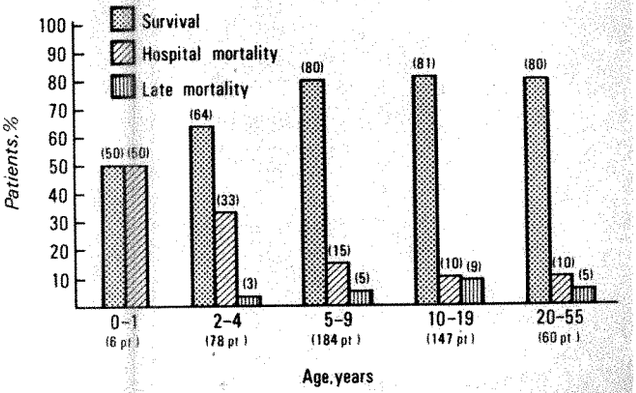


FIGURE 3. Relation between age of patient (pt) at time of intracardiac repair and survivorship, hospital mortality and late mortality. The number of patients within each age group is shown at bottom in parentheses.

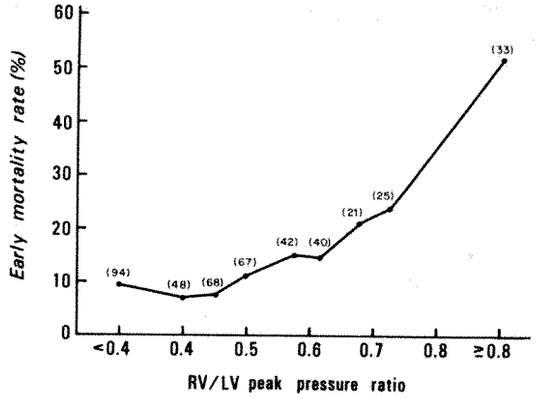


FIGURE 4. Relation between intraoperative right ventricular to left ventricular (RV/LV) peak pressure ratio and early mortality. Observe that ratios of 0.65 or greater were proportionately associated with mortality. The number of patients with each intraoperative ratio is denoted within parentheses.

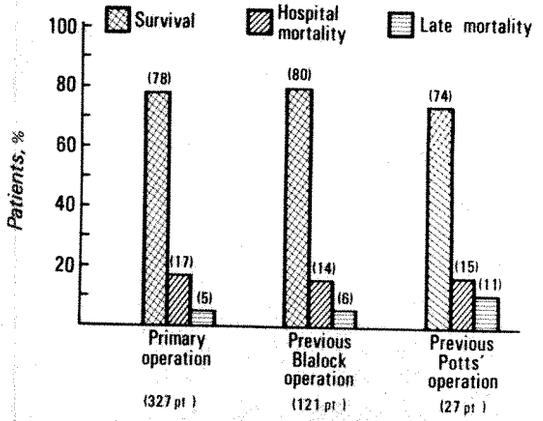


FIGURE 5. Relation between primary intracardiac operation or previous specific palliative operations followed by intracardiac repair and survivorship, hospital mortality, and late mortality. The number of patients in each surgical group is shown at bottom in parentheses.

operative RV/LV pressure ratio, or by the presence and type of prior anastomotic operation (Fig. 5); although there was a trend toward a higher late mortality rate in patients with a higher intraoperative RV/LV pressure ratio and in patients with a prior Potts' anastomosis, it did not reach statistical significance ($p = 0.14$). The specific causes of the 27 late deaths and the postoperative time of their occurrence are listed in Table V. Fifteen (71 percent) of the 21 deaths due to cardiac causes occurred within the first 2 postoperative years.

Sudden death (Table VI), without previous evidence of cardiac symptoms, occurred in 12 patients (3 percent). A possible contributing factor in four of the sudden deaths was the presence of a significant residual ventricular septal defect that in three patients was associated with significant cardiomegaly (cardiothoracic ratio greater than 0.60): In two patients a large defect was demonstrated at autopsy, in one patient the defect had been demonstrated 9 years before at cardiac catheterization (1.4:1 shunt), and in one the defect had been suspected clinically and the patient died before catheterization. One of these patients with a residual ventricular septal defect had well documented ventricular tachycardia before death; two of the other three patients had transient junctional rhythm early postoperatively but no detectable arrhythmias on routine follow-up study. In four patients the exact cause of death could not be identified clinically or at autopsy, although three of the four had significant cardiomegaly (cardiothoracic ratio greater than 0.60). One of these patients died with well documented ventricular fibrillation and another had had transient junctional rhythm early postoperatively but no detectable heart block or arrhythmias on routine follow-up study. In three patients, late sudden death was related to the operative complication of complete heart block when pacemakers were only in the initial stages of development; none of the other patients with late sudden death had preceding evidence of complete heart block or bifascicular block (right bundle branch block and left axis deviation).

Right ventricular outflow abnormalities were the cause of death in seven patients (1.5 percent) (Table V). Three patients died during reoperation for an aneurysm of the outflow patch. Possible contributing factors to the formation of the aneurysm were the Ivalon® type of patch used in the initial operation of all three patients and the higher than 0.65 RV/LV pressure ratio present after repair in two of the three. Two patients died as a result of the right ventricular outflow obstruction with right ventricular failure. In one of these patients the significant residual obstruction was known to be present at the initial operation, but for technical reasons an outflow patch could not be inserted; in the other patient no significant residual obstruction was detected at operation but was found at cardiac cathe-

TABLE III

Technique for Relief of Right Ventricular Outflow Obstruction and Hospital Mortality

Type	Patients (n)	Deaths n	Deaths %
Infundibulectomy only or with valvulotomy	262	29	11
Infundibulectomy and outflow tract patch			
Across pulmonary anulus	169	43	25
On RVOT only	44	7	16
Total	475	79	

RVOT = right ventricular outflow tract.

TABLE IV

Causes of Early Mortality

Low cardiac output	37
Complete A-V heart block	21
Bleeding	10
Respiratory insufficiency	4
Bacterial endocarditis and sepsis	3
Residual right ventricular outflow obstruction	2
Ventricular arrhythmia	2
Total	79

A-V = atrioventricular.

terization 9 years later. Finally, one patient died as a result of severe pulmonary valve incompetence and one as a result of bacterial endocarditis.

Contributing factors leading to reoperation: Nineteen patients (4 percent) required reoperation, and 14 of them are alive. In 14 of the 19 reoperation was performed because of a residual or recurrent ventricular septal defect. One of these patients died at the time of reoperation and another died 5 months postoperatively. Sixteen other patients with a residual or recurrent ventricular septal defect, all with less than a 1.5:1 shunt, did not undergo reoperation. Between 1955 and 1959, the use of an Ivalon patch for primary closure of the ventricular septal defect, in contrast to the use of direct suture repair or the later Teflon® patch, appeared to contribute significantly to the incidence of residual or recurrent defect ($p < 0.01$).

Five patients were reoperated on as a result of a right-sided outflow abnormality. Three of these patients died at the time of reoperation. The other two patients are alive; in both patients the RV/LV pressure ratio was already higher than 0.65 after the initial operation.

Specific Clinical Features of the Hospital Survivors

Postoperative heart size: Among the 246 hospital survivors who had a follow-up chest roentgenogram, cardiac enlargement, defined as a cardiothoracic ratio higher than 0.55, was observed in 60 (25 percent). However, this specifically occurred in 5 (56 percent) of the 9 asymptomatic patients and in 13 (62 percent) of the 21 who died late of cardiac causes. Of eight patients with late sudden unexpected death whose data were available, six had significant cardiomegaly: (related to a significant ventricular septal defect in three, caused by persistence of preoperative cardiomegaly in two and without apparent cause in one).

The exact contributing factors accounting for the postoperative increase in cardiac size were difficult to define because postoperative cardiac catheterization studies performed to search for residual intracardiac lesions were performed only in selected patients. Nevertheless, the apparent most important contributing factors accounting for the postoperative increase in heart size (Table VII) were preoperative cardiomegaly persisting postoperatively (about 33 percent of these patients), significant residual pulmonary valve incompetence (about 25 percent) and a significant residual ventricular septal defect (about 17 percent). A patch across the pulmonary anulus was present in 28 (46 percent) of the 60 patients with postoperative cardiomegaly and in only 50 (27 percent) of the 186 patients without postoperative cardiomegaly; this greater incidence of cardiomegaly in patients with a transanular patch was probably in part related to the residual significant pulmonary valve incompetence observed in some of these patients (11 of 28).

Pulmonary valve incompetence: All patients, after insertion of an outflow patch across the pulmonary valve anulus, have some degree of pulmonary valve incompetence. Also, some patients who undergo pulmonary valvotomy later manifest pulmonary incompetence. In our study, significant pulmonary valve incompetence contributed to some type of disability in only 3 (1 percent) of the 396 hospital survivors (1 patient who died late and 2 symptomatic patients). However, significant pulmonary valve incompetence appeared to be the most likely contributing factor for the postoperative increase in heart size in 13 (5 percent) of the 246 hospital survivors who had follow-up chest roentgenograms.

Residual pulmonary stenosis: Thirty-three of the surviving patients who had follow-up cardiac catheterization at least 1 year (range 1 to 21 years) postop-

TABLE V

Causes of Late Mortality

Cause	Patients (n)	Years Postoperatively
Sudden death	12	2 (≤1–14)*
Right ventricular outflow abnormality		
False aneurysm of patch	3†	1, 1, 1
Significant gradient	2	1, 15
Severe pulmonary incompetence	1	16
Bacterial endocarditis of patch	1	1
Ventricular septal defect (residual)	1†	1
Acute heart failure	1‡	7
Unrelated	5	8 (4–16)*
Unknown	1	8
Total	27 (6%)	

* Mean (range). † Patients died at time of reoperation. ‡ Patient died 5 years after reoperation for residual ventricular septal defect.

TABLE VI

Late Mortality—Sudden Death

Contributing Factor or Cause	Patients (n)
Heart block (since operation)	2
Heart block (since operation) with fracture of pacer lead	1
Pulmonary vascular disease (previous Potts' anastomosis)	1
Ventricular septal defect (residual)	4
Unknown	4
Total	12 (3%)

TABLE VII

Postoperative Increase in Heart Size: Contributing Factors, Late Mortality and Symptomatology

Contributing Factor or Cause	Patients (n)	Late Deaths (n)	Symptomatic (n)
Preoperative cardiomegaly	20	2	3
With prior anastomotic operation	5	2	0
Without prior anastomotic operation	15	0	3
Pulmonary valve incompetence	16	1	2
Ventricular septal defect (residual)	10	5	—
No apparent cause	7	1	—
Right ventricular outflow abnormalities	4	4	—
Reopening of previous anastomosis	2	—	—
Associated valvular heart disease	1	—	—
Total	60 (25%)	13 (62%)	5 (56%)

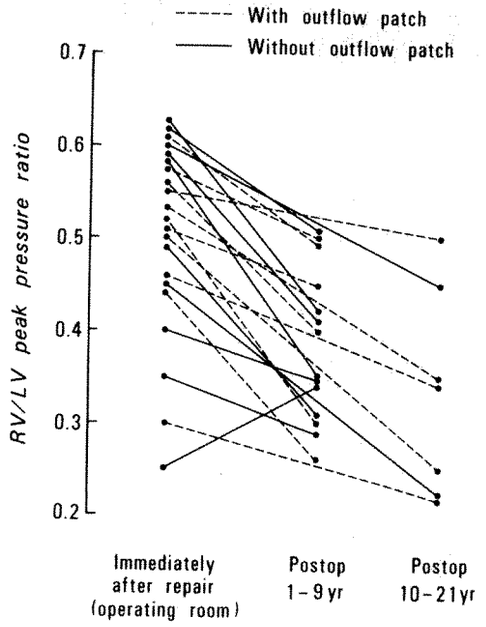


FIGURE 6. Right ventricular to left ventricular (RV/LV) peak pressure ratio in 21 patients whose ratio was less than 0.65 immediately after repair (operating room) and who underwent a second hemodynamic study between 1 and 21 years of the follow-up study (Postop). With one exception, the pressure ratio was lower in the second hemodynamic study in all patients.

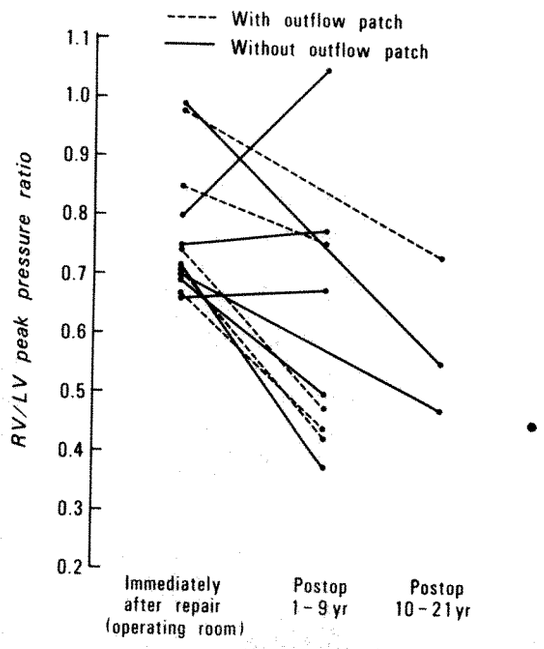


FIGURE 7. Right ventricular to left ventricular (RV/LV) peak pressure ratio in 12 patients whose ratio was more than 0.65 immediately after repair (operating room) and who underwent a second hemodynamic study between 1 and 21 years of follow-up (postop). In three of the seven patients without an outflow patch the pressure ratio did not decrease.

eratively and who showed no residual ventricular septal defect were evaluated for right ventricular outflow obstruction. The right ventricular to left ventricular (RV/LV) pressure ratio obtained at catheterization was compared with ratios obtained in the operating room after cardiac repair was completed (Fig. 6). In 21 patients with an intraoperative RV/LV pressure ratio of less than 0.65, there was a significant tendency for this ratio to decrease with the years of follow-up in both the group with and the group without an outflow patch ($p < 0.01$); in fact, none of these patients with an intraoperative pressure ratio of less than 0.65 had a ratio greater than 0.52 late postoperatively. In five patients with an outflow patch and an intraoperative RV/LV pressure ratio 0.65 or greater (Fig. 7), there was a significant tendency for this ratio to decrease with the years of follow-up ($p < 0.01$), although in two patients the ratio was still greater than 0.50. There was no significant average decrease in the elevated RV/LV pressure ratio in the seven patients without an outflow patch, although all of them were asymptomatic. An intraoperative post-repair RV/LV pressure ratio of 0.65 or greater was observed in 63 (16 percent) of the 396 hospital survivors, and specifically, in 6 (29 percent) of 21 who died late of cardiac causes and in 2 (25 percent) of the 8 whose death was sudden and unexpected ($p = 0.33$).

Electrocardiographic conduction abnormalities: A complete right bundle branch block pattern was found in 337 (85 percent) of the 396 hospital survivors. Twenty (7 percent) of the 337 patients had additional left axis deviation (bifascicular block pattern); as discussed earlier, none of these patients had late sudden death, but one had transient complete atrioventricular (A-V) block at the time of operation. An incomplete right bundle branch block pattern was found in 23 (6 percent) of the 396 patients.

Permanent complete A-V block was observed in 7 (2 percent) of the 396 patients; 3 of these patients had late sudden death and, as discussed, this occurred when pacemakers were only in the initial stages of development. The four other patients have a permanent pacemaker, implanted in two at the time of operation and in the other 2 years later when permanent complete A-V block developed. Transient complete A-V block at the time of operation occurred in 14 (3.5 percent) of the 396 patients; permanent A-V block developed years later in only 2 of these 14 patients, and as mentioned, both required a permanent pacemaker.

Discussion

This review, which is primarily a study of the clinical status of patients after repair of tetralogy of Fallot, is unique because the study group consists of one of the largest and earliest surgical series. It involves patients operated on during the first 10 years that this operation was available, and provides a follow-up review of 12 to 22 years. Aside from the higher hospital mortality rate encountered in this earliest experience, the results compare favorably with that of a later experience at this same institution involving patients operated on after the early years of rapid evolution of operative techniques.[8] Thus, 12 to 22 years following the repair, 87 percent of the hospital survivors had an excellent result, as judged by their asymptomatic status and freedom

from limitations on their usual daily activities. When contrasted with the poor life expectancy without operation,[9] the good operative result is most gratifying, despite a mild to moderate increase in heart size in some patients and despite reports that a significant number of patients after repair of tetralogy of Fallot show a good symptomatic result but have abnormal hemodynamics[10] or reduced cardiac output and heart rate response to exercise.[11-14] Because in our hospital survivors a follow-up cardiac catheterization was performed in a selected group of only 83 patients, an accurate evaluation of the postoperative hemodynamics and of the incidence of residual structural lesions could not be obtained for the total study group.

• **Hospital mortality:** The principal detractor from an excellent result was the hospital mortality rate, which was 26 percent in the period from 1955 to 1959 and has steadily decreased throughout the later years of this study. The increased mortality that occurred between 1955 and 1959 was partly due to impaired ability to avoid the production of permanent complete heart block.[15] The significantly greater hospital mortality in infants and young children than in older patients may not be relevant to the present time,[16-20] with its improved operative and postoperative methods, but it does suggest that the margin for mismanagement may be much narrower in the younger age group. Although in this early experience patients with a transanular patch had a significantly greater hospital mortality, this finding has not been documented in our most recent experience.[8]

Late mortality: Although less common than hospital mortality in this early experience, the occurrence of late death is of some concern currently, because it appeared most commonly as a sudden event and within the first 2 postoperative years. Continued study of this problem is clearly important in an effort to identify causative factors or to develop methods to minimize its hazard. Thus, sudden death occurred in 12 patients. Four of these deaths would be rare today because three were related to A-V heart block when pacemakers were only in the earliest stages of development and one was secondary to pulmonary hypertension as a result of a previous Potts' anastomosis. Of interest is the sudden death of four patients with significant size residual or recurrent ventricular septal defect and significant cardiomegaly in three of them. One of these patients had well documented ventricular tachycardia before death. Furthermore, of the remaining four patients in whom an anatomic cause of death could not be identified, three had significant cardiomegaly and one of them died with well documented ventricular fibrillation. It is then possible, as suggested by other reports,[21-23] that most sudden deaths were related to ventricular arrhythmias. Our data also suggest that in many of these patients myocardial dysfunction, as judged from significant cardiomegaly, may trigger the arrhythmia. These observations raise the possibility that follow-up cardiac catheterization to rule out a significant residual structural lesion should be performed in patients after repair of tetrology of Fallot, particularly in those with significant cardiomegaly. Patients with primary myocardial dysfunction might be subjected to a treadmill stress test and 24-hour Holter electrocardiographic monitoring to identify those who might benefit from antiarrhythmic therapy. However, the impact on mortality would be minimal because sudden, unexplained death, presumably related to cardiac arrhythmia, occurred in only four of our patients (0.8 percent), and a similar low incidence rate (0.9 percent) was also documented in our more recent patients operated on from 1965 through 1970.[8]

Not one of the patients who died suddenly had demonstrated bifascicular block. A similar lack of relation between bifascicular block and late sudden death was also apparent in the group operated on from 1965 through 1970.[8] Thus, contrary to the views of other investigators,[24-27] our data and those of others[28,29] do not justify a prognostic electrophysiologic study of the conduction system in postoperative patients with bifascicular block.

Other causes for late death or reoperation required because of incomplete closure of ventricular septal defect or insufficient relief of pulmonary stenosis are related to surgical techniques. Thus, they have been largely avoided more recently by abandonment of closure of ventricular septal defect with improper patches (Ivalon), and by willingness to use outflow patch gussets in order to avoid high residual gradients. Similarly, these technical improvements minimize the current probability that reoperation will be required.

Role of residual pulmonary stenosis versus pulmonary incompetence: The question whether patch graft reconstruction of the outflow tract is advisable in borderline situations has been dealt with extensively.[22,30-32] Over the years, the difference of opinion had focused on the ill effects of residual pulmonary stenosis versus insufficiency. The present data suggest that the immediate post-repair right to left ventricular pressure ratio is usually higher than it will be as the years of follow-up elapse, whether or not a patch reconstruction is used. However, in patients in whom the immediate post-repair pressure ratio is highest (0.65 or greater), there is a risk, for those in whom an outflow patch is not used, that the pressure ratio will not decrease with time (three of our seven patients), that reoperation will be required (two other patients) or that even death might ensue (one other patient). Moreover, as documented by others,[33] the outflow gradients can increase markedly during exercise.

The insertion of an outflow patch across the pulmonary valve anulus always results in some degree of pulmonary valve incompetence. However, recent hemodynamic data[34,35] indicate that the majority of patients tolerate this lesion well for many years and that their response to exercise remains adequate if there is no significant residual obstruction. Indeed, in our long-term study, pulmonary incompetence has contributed to only 1 late death, to the symptoms of 2 patients, and probably, to the mild increase in heart size of 13 of the 246 patients who had follow-up chest roentgenograms. For these reasons, thus far we do not favor use of more recently introduced techniques of insertion of substitute pulmonary valves or outflow tract conduits, except in patients with impaired pulmonary arterial runoff

caused by peripheral stenosis, vascular obstructive disease, single pulmonary artery or agenesis of pulmonary valve with aneurysm of the central pulmonary arteries.

Role of residual anatomic and functional abnormality: Of particular concern with respect to the late result of corrective operation for patients with tetralogy of Fallot is the usual failure of correction to restore the heart to normalcy. Residual anatomic and functional abnormality exists, particularly at the right ventricular outflow tract level, and to some extent the right ventricular myocardium may be permanently altered. Thus, because asymptomatic patients may have a poor hemodynamic result, their lack of symptoms must be viewed with some caution. However, if these residual alterations were to exert a significant, time-related adverse effect on the late result of operation, a downturn in the actuarial survival curves should occur by 20 years after operation. The absence of such a downturn in our study (Fig. 1) is highly gratifying.

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Cardiac Malformations in the Velocardiofacial Syndrome

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A similar pattern of congenital anomalies found in 27 children, 9 male and 18 female, aged 2 weeks to 17 years, allows the conclusion that they represent a newly recognized malformation syndrome. All patients had velopharyngeal insufficiency, a submucous or overt cleft of the secondary palate and learning disabilities. A similar facies, characterized by a long vertical face, a large fleshy nose with broad nasal bridge, flattened malar region, narrow palpebral fissures and deep overbite with retruded mandible, was usually present. Other noncardiac anomalies also occurred frequently. Twenty-three (85 percent) had congenital cardiovascular malformations whose occurrence as single or combined lesions far exceeded the expected incidence in children with congenital heart disease. A ventricular septal defect was present in 15, tetralogy of Fallot in 5. Prolapse of the right aortic cusp was present in two patients with a ventricular septal defect, and aortic valve disease with insufficiency in one patient with tetralogy. The aortic arch was right-sided in 12 patients, in conjunction with a ventricular septal defect in 5, in association with tetralogy of Fallot in 4 and in the absence of associated cardiac disease in 3. The right aortic arch descended on the right in 10 patients; in 2 with a ventricular septal defect it crossed retroesophageally to descend on the left, and in one of these it presented as the "third aortic arch syndrome." Aberrant origin of the left subclavian artery was present in five patients with a right aortic arch. A patent ductus arteriosus had caused congestive heart failure in infancy in one patient with a small ventricular septal defect; three others with a ventricular defect had additional clinically minor anomalies. Two children were brother and sister. Their mother and the mothers of two other children showed evidence of the same syndrome, suggesting the possibility of autosomal dominant or X chromosome-linked dominant transmission.

In an earlier report[1] we described 12 children with a pattern of similar malformations believed to represent a newly recognized congenital malformation syndrome. Although other manifestations with varying frequency were noted, most consistently present were overt or submucous clefts of the secondary palate, typical facies, learning disabilities and ventricular septal defect; hence, the designation velocardiofacial syndrome. The occurrence in all patients of velopharyngeal insufficiency, generally reflecting poor motion in the lateral pharyngeal walls, necessitated specific surgical correction.

Twenty-seven children with this syndrome have now been evaluated in this center. Twenty-three have shown cardiovascular anomalies. This report details our observations in these 23 patients and presents an unusual conformity of cardiac involvement.

Methods

Patients: Of the 27 children 9 were male and 18 female. Their ages on initial referral ranged from 2 months to 17 years. Twenty-two were referred because of hypernasal speech, usually considered of unknown origin. Two were neonates referred because of clefts of the velum and suspected Robin malformation complex.[2] Three were initially seen for cardiac evaluation, at which time the diagnosis of velocardiofacial syndrome was made. Cardiovascular disease had been recognized or suspected in 16 before their coming under our care.

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Detailed histories for possible teratogenic or environmental influences or familial genetic factors were obtained on all patients. Chromosomal studies were obtained in four patients.

Diagnostic procedures: The cardiac diagnosis, established by physical examination, electrocardiogram and roentgenograms of the chest in all, was confirmed by cardiac catheterization and angiocardiography in 17 and at cardiac surgery in 9. Thirteen had undergone previous diagnostic cardiovascular study elsewhere. Repeat studies were obtained in one of these and initial cardiac catheterization was performed in four patients in our institution. Seven had undergone previous cardiac surgery elsewhere and two patients were operated on in our institution. All catheterization data, angiocardiograms and operative reports were reviewed.

Results

Noncardiac Malformations

The noncardiac malformations present are listed in Table I. Most frequent were hypernasal speech with overt or submucous clefts of the secondary palate, similar facies and specific learning disabilities, usually involving the ability to form abstractions, mathematical ability and visual-motor capacity. Only 12 patients were significantly retarded. All of the intellectually impaired patients were in the educable range with the exception of one trainably retarded patient.

The most striking feature of these patients was the similar facies (*Fig. 1*). This was characterized by a large, fleshy nose with a broad nasal bridge, flattened malar region, narrow palpebral fissures, deep overbite with a class II malocclusion and retruded mandible, abundant scalp hair and a vertically long face.

Chromosomal studies were normal in all patients whose karotypes were obtained. Three instances of familial occurrence of the syndrome were recognized. The mother of one girl with a ventricular septal defect showed a similar facies, a large U-shaped palatal defect with hypernasal speech, a retruded mandible and learning disabilities, but no cardiovascular abnormalities. The mother of another girl with a ventricular septal defect also had a similar facies with microcephaly and a submucous palatal cleft. Two patients with tetralogy of Fallot were brother and sister. Their mother was retarded, showed a palatal cleft, typical facies and a normal heart and aorta.

Four unaffected mothers had received progestational agents during the early first trimester of pregnancy. In addition, one mother was an operating room nurse who had been exposed to anesthetic gases during pregnancy.

TABLE I

Velocardiofacial Syndrome: Noncardiac Malformations in 27 Patients

	n	%
Submucous cleft of secondary palate	19	70
Overt cleft of secondary palate	8	30
Learning disabilities	27	100
Hypotonia in infancy	23	85
Narrow palpebral fissures	21	78
Retruded mandible	19	70
Malar flatness	19	70
Auricular anomalies	19	70
Prominent nose	18	67
Slender hypotonic hands	14	52
Microcephaly	12	44
Mental retardation	12	44
Small stature	11	41
Inguinal hernia	5	27
Vertebral anomalies	3	11

Cardiovascular Malformations

Congenital cardiovascular malformations were demonstrated in 23 (85 percent) of the 27 patients (Table II).

Ventricular septal defect: A ventricular septal defect was present in 15 patients (65 percent). Ten had a normal left aortic arch and five (33 percent) a right aortic arch. One patient, first seen at age 6 years with an isolated right-sided aorta and mild left ventricular enlargement in the chest roentgenogram, had a history of a heart murmur in infancy. He may have had spontaneous closure of a ventricular septal defect at an earlier age.

Two of the five patients with a ventricular septal defect and right aortic arch also showed prolapse of the right aortic cusp. In one, aortic insufficiency was not clinically apparent but prolapse was demonstrated

TABLE II

Velocardiofacial Syndrome: Cardiovascular Malformations in 27 Patients

Predominant Malformation Type	n	Associated Malformation Type	n
Normal heart			
Normal aortic arch	4	. . .	. . .
Right aortic arch	3	Aberrant left subclavian artery	1
Ventricular septal defect			
Normal aortic arch	10	Valvular and infundibular pulmonary stenosis	1
		Patent ductus arteriosus	1
		Aberrant right subclavian artery	1
		Left superior vena cava	1
Right aortic arch			
No retroesophageal component	3	Aberrant left subclavian artery	2
		Prolapsed aortic cusp	1
Retroesophageal component	2	Aberrant left subclavian artery	2
		Prolapsed aortic cusp	1
		"Third aortic arch syndrome"	1
Tetralogy of Fallot			
Left aortic arch	1	Left superior vena cava	1
Right aortic arch (not retroesophageal)	4	Aberrant left subclavian artery with left patent ductus arteriosus; aortic insufficiency	1
Total	27		14



FIGURE 1. Characteristic facies in children with the velocardiofacial syndrome. Note the large fleshy nose with a broad nasal bridge, flattened malar region, vertical long face, retruded mandible, auricular malformation and abundant hair. The patient in the panels **at bottom** demonstrates narrow palpebral fissures with a downward obliquity.

angiographically. In the other patient aortic insufficiency was marked.

Cardiac catheterization was performed in 11 patients with a ventricular septal defect. The ratio of pulmonary to systemic blood flow ranged from 1.4 to 2.6. The shunt was demonstrable only on angiocardiography in three. Pulmonary vascular resistance was normal in all.

Tetralogy of Fallot: Five patients (21 percent) presented with tetralogy of Fallot, and four (80 percent) of these had a right aortic arch. One probably originally had a large ventricular septal defect that was altered to tetralogy as a result of progressive infundibular hypertrophy.

Right aortic arch: A right-sided aortic arch was present in 12 patients (52 percent). Four of the 12 had no evidence of heart disease. In three of the four the arch was anterior and to the right of the esophagus, descending on the right with no retroesophageal component. In the fourth patient the angiogram revealed the branches of the aorta to be the left common carotid, the right common carotid and the right subclavian arteries, with the left subclavian artery arising as the fourth branch from the left dorsal aspect of the upper descending aorta, crossing behind the esophagus and indenting its posterior wall.

Of the five patients with ventricular septal defect and a right-sided aortic arch, three manifested an aorta that descended on the right and had no retroesophageal component. One of these three also had an aberrant left subclavian artery crossing the mid line behind the esophagus.

The remaining two manifested a right aortic arch with a retroesophageal component and descent of the aorta on the left. One showed a cervical position of the right-sided aortic arch ("third aortic arch syndrome") from which the first three great vessels arose, respectively, as the left common carotid, the right common carotid and the right subclavian artery, with the left subclavian artery arising as the fourth brachiocephalic vessel from a diverticulum at the junction of the right aortic arch and upper descending aorta. In the second patient, who also had a prolapsed right aortic cusp, the left subclavian artery also arose aberrantly as the fourth branch of the aorta.

Four patients with the tetralogy of Fallot had a right aortic arch and descending aorta. Three showed mirror-image branching of the brachiocephalic vessels. However, one had an aberrant left subclavian artery with a patent ductus arteriosus connecting it to the left pulmonary artery to form a vascular ring.

Other cardiovascular abnormalities: Most additional cardiac malformations were of no physiologic significance (Table II). One child with a ventricular septal defect who had had congestive heart failure in infancy showed mild valvular and infundibular pulmonary stenosis with a right ventricular-pulmonary artery gradient of 25 mm Hg at age 5 years. Another with a small ventricular septal defect had had congestive failure in infancy primarily because of a large patent ductus arteriosus. The patient with tetralogy, right aortic arch and vascular ring also had a thickened aortic valve with aortic insufficiency.

Bacterial endocarditis had occurred in one patient. One patient with a right aortic arch and no evidence of structural heart disease showed varying nodal rhythm and atrioventricular dissociation; these abnormalities posed no problem during her palatal surgery.

Discussion

Incidence of cardiovascular malformations associated with facial clefting: Cardiac lesions in association with facial clefting were considered relatively rare by McKeown and Record.[3] Among 55,539 live births, there were only 5 such patients, all of whom died in the 1st month of life. Shah et al.[4] reported a 1.3 percent incidence rate of congenital heart defects in 150 living patients with facial clefts. Of these 10 patients, 3 had an isolated ventricular septal defect and 2 a ventricular septal defect in conjunction with other cardiac defects. None had a right aortic arch.

In our Center for Craniofacial Disorders, of 275 patients with an isolated cleft palate, not part of other malformation syndromes, 7 children (2.5 percent) have shown evidence of congenital heart disease: 3 with coarctation of the aorta (including 1 with ventricular septal defect and patent ductus arteriosus) and 1 each with secundum atrial septal defect, aortic stenosis, pulmonary stenosis and patent ductus arteriosus.

Incidence of cardiovascular malformations in velocardiofacial syndrome: The incidence of cardiovascular malformations, either as single or combined lesions in this group of patients with the velocardiofacial syndrome, far exceeds the expected incidence in children with congenital heart disease. Among 56,109 births recorded by Mitchell et al.,[5] 457 infants had congenital heart disease. A ventricular septal defect was present in 29 percent, tetralogy of Fallot in 3.5 percent and a right aortic arch and patent ductus arteriosus in two infants. At a median age of 3 years in those with congenital heart disease, the incidence rate was 40 percent for ventricular septal defect and 4 percent for tetralogy. In Keith's long term follow-up[6] the respective incidence rates were 28 and 11 percent. On the basis of examination of a large series of chest roentgenograms the incidence rate of isolated right aortic arch has been reported to be approximately 0.1 percent.[7] Among 116 children and young adults with a right aortic arch the anomaly was unassociated with congenital cardiac disease in only 4 (3 percent). The reported incidence rate of a right aortic arch in patients with tetralogy of Fallot ranges from 13[8] to 34 percent,[7] and in patients with an isolated ventricular septal defect from 2[9] to 6 percent.[10] Aortic insufficiency, usually due to a prolapsed right aortic cusp, has been reported to occur in 2[11] or 3 percent[12] of patients with a ventricular septal defect.

Intracardiac anomalies associated with right aortic arch: In light of other reported experiences, our 12 patients with a right aortic arch also had an unusual incidence of associated intracardiac anomalies. When

the aorta ascends on the right and descends anteriorly and to the right of the trachea and esophagus, congenital heart disease is almost invariably present.[13,14] In contrast, in our group with ascent and descent of the aorta on the right, three had no evidence of heart disease.

When the aorta ascends on the right and crosses posterior to the esophagus to descend on the left, associated intracardiac disease is extremely uncommon.[13,14] However, a ventricular septal defect was present in our two patients with a right-sided ascending aorta and a retroesophageal segment and in both patients the left subclavian artery arose as the fourth branch from the descending aorta. In one patient, as commonly occurs, the ascent of the right aortic arch was higher than normal, but the apex of the arch was below the clavicle. The other patient had a cervical aortic arch—an uncommon cardiac malformation that has been described in only 18 patients, none of whom had an intracardiac defect.[15]

Comparison with other cardiofacial syndromes: Exclusive of cardiofacial abnormalities resulting from known chromosomal defects or from known teratogenic agents, three "cardiofacial"syndromes merit comment for comparison.

Patients with the Williams' syndrome[16] present with supravalvular aortic stenosis, mental retardation and a characteristic facies typified by widely spaced eyes; broad, depressed nasal bridge; heavy cheeks; a wide mouth with course pouting lips, and elfin-like ears. Patients with presumed variants of the Williams' syndrome, all with mental retardation and similar facies but with pulmonary valvular dysplasia,[17] supravalvular pulmonary stenosis[18] or discrete subvalvular aortic stenosis,[19] have also been described.

In the Noonan syndrome[20,21] there is commonly, although not invariably, mental retardation and a facies characterized by hypertelorism; a short, webbed neck; low-set ears; and a low posterior hairline. Cardiac manifestations are usually pulmonary stenosis with or without an atrial septal defect,[21] cardiomyopathy[22] or asymmetric septal hypertrophy.[21,23]

In neither syndrome does the facies resemble that of patients with the velocardiofacial syndrome or is palatal clefting present. A right aortic arch has not been noted in any patient with either syndrome; ventricular septal defect has occurred only infrequently in the Noonan syndrome.[21]

The DiGeorge syndrome, or third and fourth pharyngeal pouch syndrome,[24,25] although characterized by absence or hypoplasia of the thymus and parathyroids with cellular immune deficiency and hypocalcemia, has many features resembling those seen in the velocardiofacial syndrome. Clefts of the lip, palate or uvula may occur. Most patients who survive infancy are mildly to moderately retarded. The facies, although somewhat similar (hypertelorism, low-set malformed ears and a short jaw), shows a shortened philtrum causing a "fish mouth." Cardiac malformations relate primarily to anomalies of the third and fourth branchial arches and there is an unusually high incidence rate of interrupted aortic arch, persistent truncus arteriosus, aberrant right subclavian artery and right aortic arch with or without intracardiac malformations.

Familial and other etiologic factors: In most of our patients the syndrome presented as a sporadic occurrence in an otherwise normal family. However, there were three instances of familial occurrence. In all three patients, the features were transmitted maternally in a dominant pattern. The etiology of the velocardiofacial syndrome based on these cases of familial transmission would appear to be genetic, and more specifically dominantly inherited. Because these familial cases were transmitted maternally, it is not possible to determine if the gene is autosomal or X chromosome-linked. However, the severity of the syndrome is fairly similar among male and female children. Thus, even though X chromosome-linked dominant transmission is possible, it would tend to support probable autosomal dominant transmission.

The large number of sporadic cases may be explained in several ways. Because the patients are intellectually impaired, there is reduction of the genetic fitness of many persons with the syndrome who, therefore, become unlikely to reproduce. Most of the patients are still below reproductive age, thus limiting the current opportunity to observe the possible effects of a dominant gene.

Finally, we cannot rule out etiologic heterogeneity. There were four unaffected mothers who had been given progestational agents during the early first trimester of pregnancy and one who had been exposed to anesthetic gases during pregnancy. The possible teratogenic effects of these substances in relation to the development of the velocardiofacial syndrome is possible but unproved.

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Update on Oral Anticoagulation

TREATING MYOCARDIAL INFARCTION AND REDUCING THE THREAT OF THROMBOEMBOLISM

Each year in this country approximately one million people suffer acute myocardial infarctions. Rapid emergency treatment in coronary care units has been credited with reducing by up to one third the mortality among patients hospitalized with acute attacks.[1]

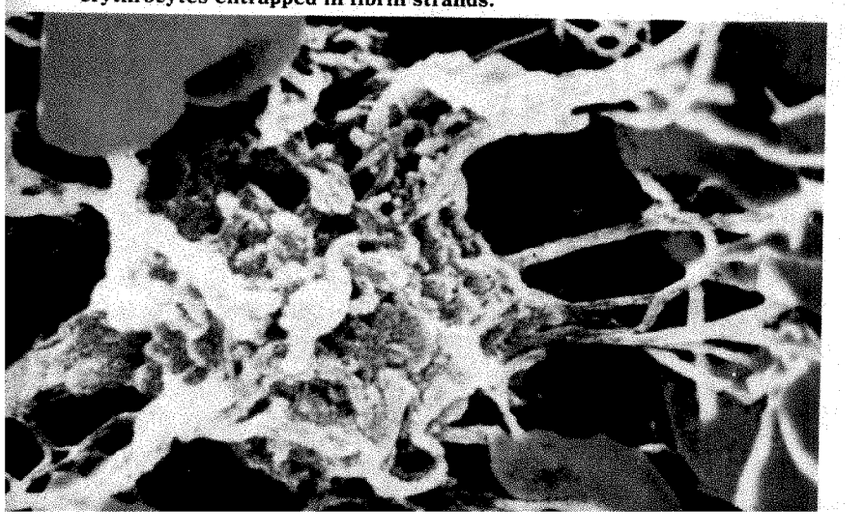
Thrombosis—incidence in myocardial infarction Following the damage to the heart itself, thromboembolism is perhaps the most serious sequel to myocardial infarction.

A study has demonstrated that there is a 39% incidence of calf vein thrombosis during the acute phase of myocardial infarction.[1]

Speed saves lives It has been reported that more than half the thrombi destined to occur in the calf veins form within 72 hours of myocardial infarction, and three-fourths form within the first week. Therefore, a number of investigators have recommended that antithrombotic measures should begin upon admission to the hospital and be effective almost immediately.[2]

Oral anticoagulants have a clinical value It has also been stated that the use of anticoagulants may reduce the frequency of calf vein thrombosis from 22 to 6.5%. The use of anticoagulants is subject to differing opinions regarding improved survival. A number of authorities recommend the use of anticoagulants in *all* patients who have no specific contraindications during the period of hospitalization.[1]

Scanning electron micrograph of 'Red' thrombus, formed by erythrocytes entrapped in fibrin strands.



One team of investigators in M.I. recommends pr viding full-dose warfarin while the patient is in th hospital and for several days afterward—

if the patient has had prior infarcts or thromboembolism
if the area of infarction is large
if complications (such as CHF or hypotensio require prolonged bed rest.

But, if post myocardial infarction syndrome (Dressler's syndrome) develops, anticoagulants should be discontinued, as pericardial hemorrhage even cardiac tamponade may develop.[1]

Objectives and benefits of anticoagulation T use of anticoagulants in the acute phase of myocar dial infarction has these potential advantages:[2]

prevention of deep vein thrombosis
reduction of embolization from cardiac mural thrombi
prophylaxis against extension of myocardial necrosis or long-term recurrence of infarction
reduction of overall mortality

If anticoagulants can inhibit the formation of deep vein thrombi, then the incidence of pulmonar embolism might be diminished—and pulmonary em lism has been estimated as a threat to life in 5,000 of the 500,000 myocardial infarction patients who are admitted to hospitals in this country each year

A look at survival One retrospective study of the use of anticoagulants in M.I. evaluated the survival of 1,307 patients from 20 hospitals in a large metropolitan community. The diagnosis of M.I. was based on predefined criteria, which includ typical chest pain, serial ECG's, enzyme elevations, and autopsy findings.

Among anticoagulated patients, the adjusted in-hospital case-fatality rate was 18%. For patients who did not receive thi treatment, the fatality rate was 31%. For survivors followed for as long as ten years patients who had been anticoagulated still fared better than those not so treated.[3]

The authors of this study recognize

the drawbacks of using retrospective evidence and call for the formation of a multi-center, double-blind, randomized study on the use of anticoagulants in acute myocardial infarction.

Screening the high risk group The risk of DVT (deep vein thrombosis) is particularly great among certain patient groups:

- patients with left ventricular failure
- patients in shock
- patients with arrhythmias
- older patients
- obese patients
- patients with varicose veins
- patients with previous myocardial infarction or thromboembolism

Screening techniques Diagnosis of DVT by physical examination may miss a significant number of clinically silent thrombi. There are, however, additional technological tools to help the clinician define more accurately the incidence of deep vein thrombosis. Among these are:

iodine-125 fibrinogen scanning—radioactively tagged fibrinogen is incorporated into actively forming thrombi and is detected on external sensors. This method is accurate for popliteal and calf vein thrombi, but not for iliofemoral thrombi.[2]



Phlebogram showing occlusion in deep vein of the upper calf.

venography—radiographic evidence of DVT is seen as a constant filling defect in venous projections, abrupt termination of a column of contrast material at a constant site, nonfilling of the deep veins, and presence of flow in collateral veins.[4]

ultrasound—Doppler ultrasound scanning can provide a fast, convenient, inexpensive reading of deep venous obstruction. This technique is potentially the most versatile and accurate method available. However, it demands considerable operator experience to insure maximal accuracy.[5]

impedance plethysmography—this technique results from the observation that blood volume changes in the calf produced by inflation or deflation of a thigh cuff produce variations in electrical resistance (impedance). Such changes are reduced in patients with thrombosis of the popliteal or more proximal veins.[4]

Patient compliance through education Providing the anticoagulated patient with information about his altered physical state and motivating him to comply with the therapeutic regimen constitute one of the most important aspects of health care.[6]

To determine the best way of imparting necessary information about anticoagulation to patients, a test was devised. One group of patients was given a brochure detailing the need for the medication and the importance of following the doctor's instructions. A second group of patients was given a programmed instruction booklet which was quite comprehensive in its teaching content, which included the action of warfarin, the purpose of prothrombin times, how to figure dosage from tablet strengths, possible complications and steps to take to control them.

When tested for learning and retention, the patients in the programmed instruction group scored significantly higher than the group given brochures only. In an area of medicine that relies so heavily on patient compliance, this report could be important in determining how medical information is communicated to the patient.[6]

The bottom line A postmortem study[7] underlines the importance of thrombosis in myocardial infarction. In this study of 173 patients with recurrent myocardial infarction, coronary occlusion due to thrombosis occurred in 54% of cases. Recent occlusive coronary thrombosis was 4 times less frequent in patients who received adequate anticoagulation (mean prothrombin level was 29 ± 5%).

And as one authority states:

"Rational use of anticoagulant therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country. Full advantage should be taken of this therapeutic opportunity."[2]

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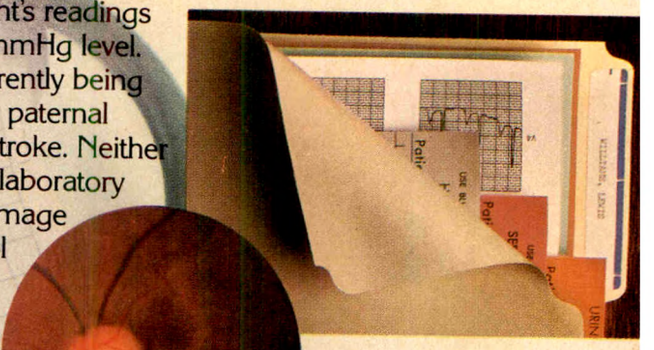
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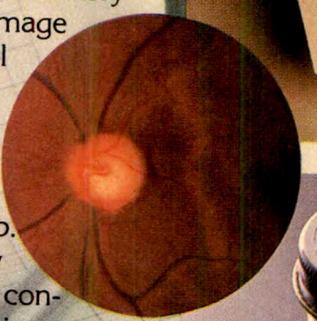
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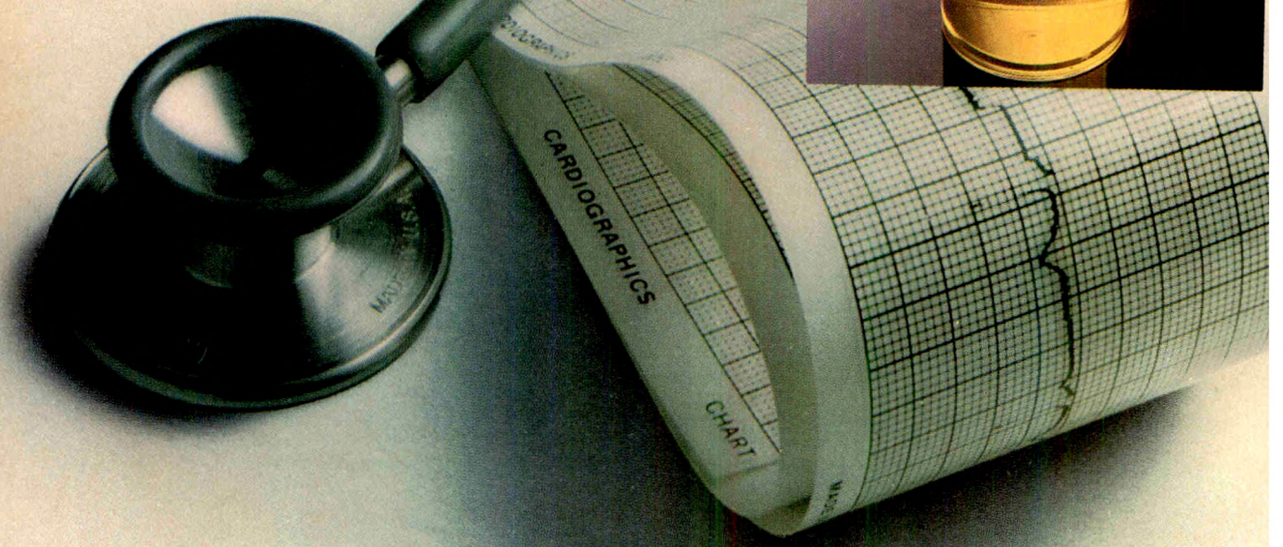
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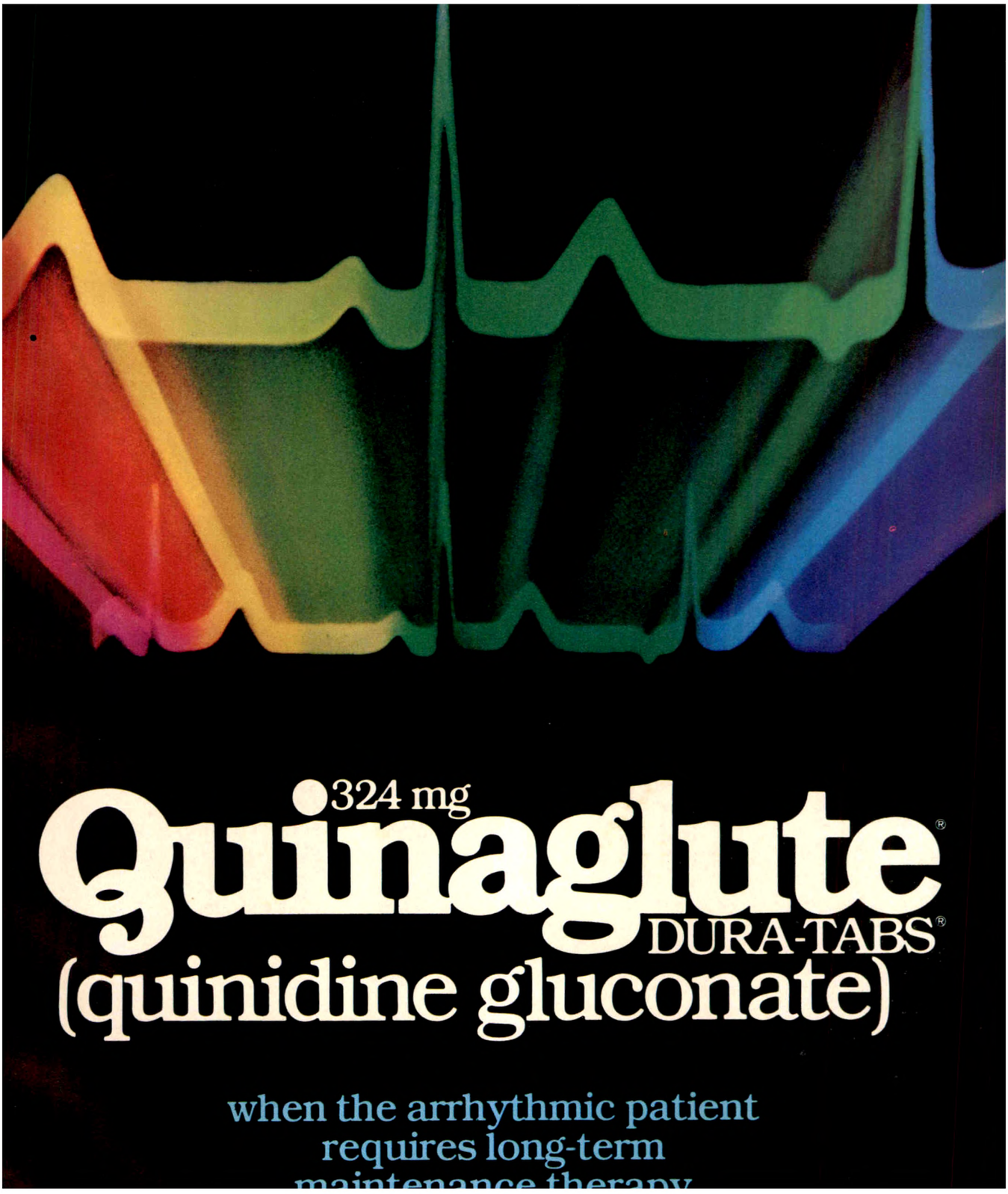
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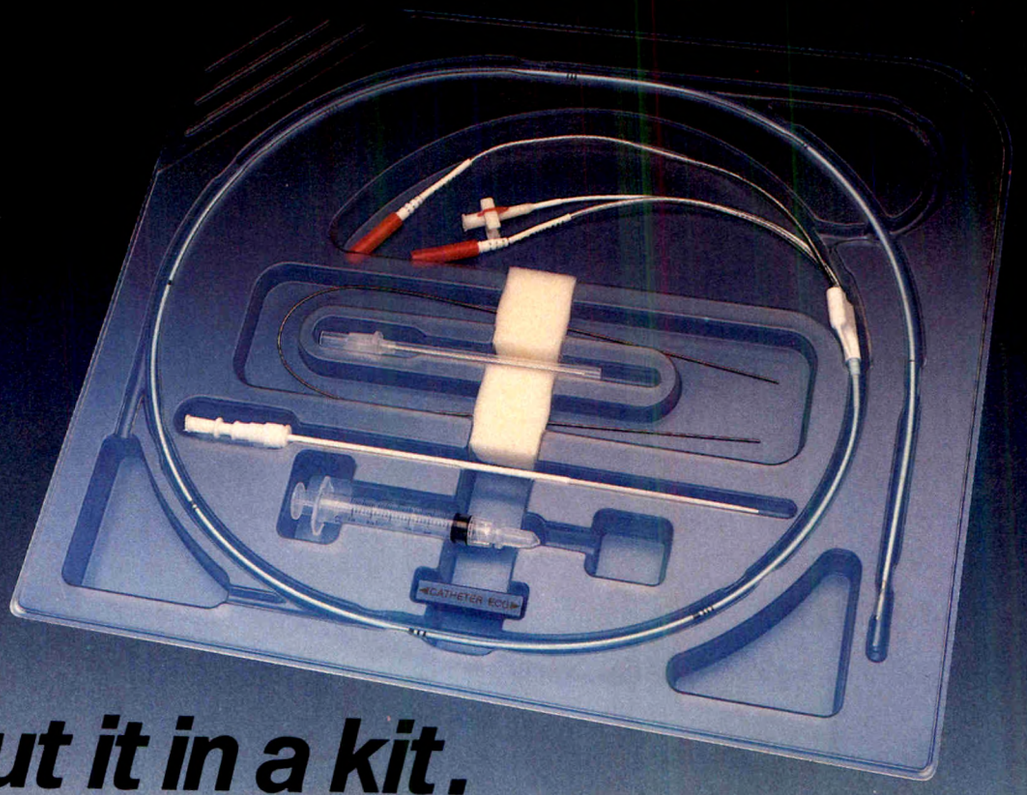
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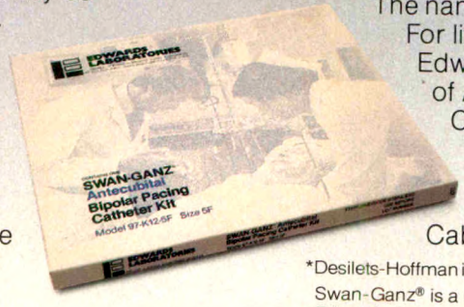
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Forty-three of 1,312 men aged 35 to 54 years in the Framingham Offspring Study had clinically recognized coronary heart disease at the initial examination. Twenty-six men in this group had previously had a myocardial infarction. Of 1,296 women in the same age range, only 11 had coronary disease and 3 a prior myocardial infarction. The prevalence of coronary heart disease in men was strongly associated with age, smoking, high density lipoprotein (HDL), low density lipoprotein (LDL) and total cholesterol using univariate analyses. When multivariate logistic regression analysis was used, age, smoking and HDL and LDL cholesterol retained their significant association with coronary heart disease. The total cholesterol/HDL cholesterol ratio was also strongly associated with coronary heart disease in the multivariate analysis. It is concluded that both HDL and LDL cholesterol are strongly and independently associated with the prevalence of coronary heart disease, whereas the level of very low density lipoprotein cholesterol makes no statistically significant independent contribution.

The relation of serum lipid and lipoprotein levels to clinically recognized coronary heart disease is an area of increasing research. Much of our understanding of the epidemiology of cardiovascular disease has accrued from the experience of several long-term prospective studies in which cases have been documented and related to commonly measured variables such as smoking, blood pressure and serum cholesterol concentration. However, many of the recent studies lacked lipoprotein cholesterol data for men and women less than 50 years old. Not enough is known about the relation between lipids and coronary heart disease in the younger population. One recently reported study[1] showed little relation between HDL cholesterol level and coronary heart disease in a group of men under age 45 years. Similarly, data are scarce relating, with use of multivariate techniques, the prevalence of these diseases to factors such as blood pressure, smoking, obesity, alcohol consumption and lipoprotein cholesterols.

This study is based on data obtained at the first examination of the Framingham Offspring Study. The results for prevalence of coronary heart disease and myocardial infarction are reported. Multivariate analysis was performed using coronary risk factors and various lipoprotein cholesterol subfractions in an effort to determine the association of these variables with cardiovascular outcomes in this relatively young population.

Methods

Study group: The study design, methodology and description of the Framingham Offspring Study sample are provided elsewhere.[2,3] The results of this report are confined to men and women aged 35 to 54 years when examined in 1971 to 1975. All subjects were either offspring (1,688 participants) or spouses of the offspring (918 participants) of the original Framingham Heart Study cohort. The historical data collected included history of coronary heart disease, smoking habits and alcohol use recorded at the time of a clinic visit that included

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a physical examination. Serum lipoprotein cholesterol levels were measured with the Lipid Research Clinic protocol, and an electrocardiogram at rest was performed at the examination.

Cholesterol determinations: Serum cholesterol was measured using a manual Abell-Kendall procedure.[4] A heparin manganese-chloride precipitation technique was used to determine the high density lipoprotein (HDL) cholesterol.[5] Low density lipoprotein (LDL) cholesterol was calculated by subtracting the HDL cholesterol from the bottom fraction cholesterol, measured after reconstitution of the bottom fraction after preparative ultracentrifugation of ethylenediamine tetraacetate plasma at serum density. The very low density lipoprotein (VLDL) cholesterol was measured by subtracting the bottom fraction cholesterol from the total cholesterol. The ratios of total cholesterol to HDL cholesterol and of LDL cholesterol to HDL cholesterol were calculated for each subject. Height and weight for each participant were determined with the subject dressed in an examining gown, wearing no shoes.

Historical data: The medical history included specific questions designed to elicit the usual consumption of alcohol. Intake of beer (number of 12 ounce cans × 0.44), wine (number of 4 ounce glasses × 0.40) and cocktails (1.5 ounce liquor × 0.57) intake was summed to achieve an overall measure of weekly alcoholic consumption.[6] The Metropolitan Life Insurance relative weight was calculated for each person from published tables.[7] The criteria for the diagnosis of myocardial infarction and coronary heart disease used in this study are described elsewhere.[8]

Statistical analysis: The univariate relation between coronary heart disease and various factors was tested by the *t* test assuming equal variances. The chi-square test was utilized for cigarette smoking. The statistical tests for the association of the specific independent variables with the dependent variable coronary heart disease employed multivariate logistic regression using the Walker-Duncan estimation method.[9] No regression analyses were performed for the women because there were too few cases of myocardial infarction or coronary heart disease.

Results

Prevalence of coronary heart disease: Among the 1,312 men examined in the Framingham Offspring Study who were 35 to 54 years old, 43 had had coronary heart disease, and 26 had a history of myocardial infarction. Among 1,296 women participants in the study in the same age range, 11 had coronary heart disease, including 3 with a myocardial infarction. There were no instances of coronary heart disease in offspring less than 35 years old at the time of the examination. The age- and sex-specific prevalence rates summarizing these results are presented in Table I. Next to these results are those for participants in the original Framingham cohort when they were sampled in 1948 to 1951.

The age-adjusted rates of coronary heart disease given for each of the sex-specific groups in Table I allow comparison between parents and offspring. The rate for men in the original cohort was 18/1,000. After direct adjustment to the cohort age distribution, the rate for the offspring was 29/1,000. The age-adjusted prevalence rates of coronary heart disease for women were 7/1,000 in the original cohort and 8/1,000 in the offspring. Because the data suggested differences between the cohort and the offspring, Mantel-Haenszel chi-square statistics were calculated using 5 year age stratifications to compare the men in the cohort with the men in the offspring ($\chi^2 = 3.80$) and the women in the two groups ($\chi^2 = 0.01$).

Coronary heart disease and abnormal lipoprotein profile: Some of the men and women with coronary heart disease had abnormal lipoproteins when classified according to the Fredrickson criteria.[5] These data are summarized in Table II for the separate Fredrickson classes, coronary heart disease diagnoses and sex. Among the 43 men with coronary heart disease, type IV hyperlipoproteinemia occurred in 11 and was twice as common as type II (5 men). Of the 11 women with coronary heart disease, 2 had type II and 1 had type IV hyperlipoproteinemia. The sole woman with a history of myocardial infarction who had an abnormal lipid profile was classified as having type II hyperlipoproteinemia.

TABLE I

Prevalence of Coronary Heart Disease (CHD) in the Framingham Cohort (1948–1951) and Offspring (1971–1975)

Age (yr)	Cohort Total (n)	Cohort With CHD (n)	Cohort Crude Rate*	Offspring Total (n)	Offspring With CHD (n)	Offspring Crude Rate*
			Men			
30–34	384	3	8	409	0	0
35–39	443	4	9	381	4	11
40–44	422	3	7	368	7	19
45–49	357	6	17	326	14	43
50–54	374	20	54	235	18	76
Total	1980	36	18	1719	43	25 (29)†
			Women			
30–34	443	0	0	472	0	0
35–39	584	1	2	364	0	0
40–44	511	3	6	388	2	5
45–49	451	5	11	351	4	11
50–54	432	8	19	193	5	26
Total	2421	17	7	1768	11	6 (8)†

* per 1000. † Numbers in parentheses represent age-adjusted rates. The offspring rates were adjusted to the cohort population using the direct method.
n = number.

TABLE II

Men and Women With Coronary Heart Disease (CHD) and Myocardial Infarction (MI) and With Abnormal Lipoprotein Profiles: Framingham Offspring

Fredrickson Lipoprotein Classification	Men CHD	Men MI	Women CHD	Women MI
II	5	3	2	1
IV	11	6	1	0
V	1	1	0	0
Normal	26	16	8	2
Total	43	26	11	3

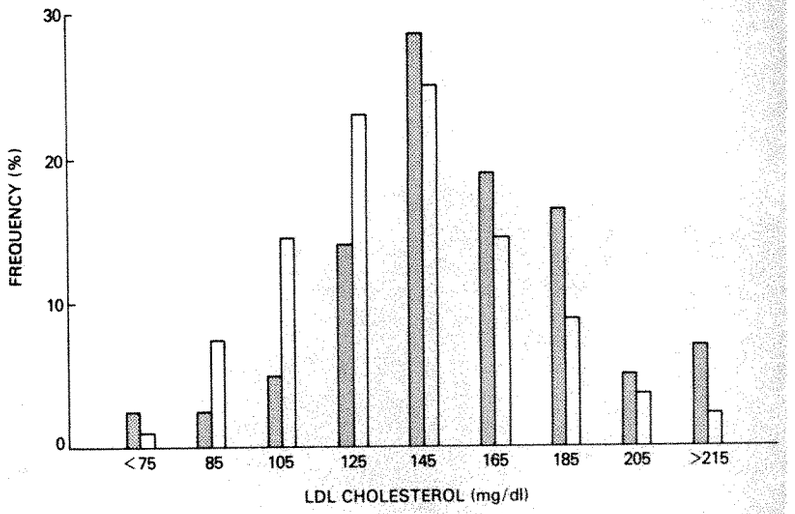


FIGURE 1. Frequency distributions of LDL cholesterol levels in men with (**stippled bars**) and without (**white bars**) coronary heart disease: Framingham male offspring aged 35 to 54 years.

Individual variables in coronary heart disease: The mean values for several variables measured for subjects with and without coronary heart disease are given in Table III. Univariate *t* tests were used to test for differences between the means. The mean values for total cholesterol, LDL cholesterol, HDL cholesterol and total cholesterol/HDL ratio showed significant differences in the two groups as did age at examination and reported cigarette use. Subjects with coronary heart disease had higher values for total and LDL cholesterol, but lower values for HDL cholesterol than those of the subjects without coronary disease.

A history of current or previous smoking was much more prevalent in the group with than in the group without coronary heart disease (95 percent versus 72 percent). The other variables tested showed no signficant differences in the two groups.

Multivariate regression coefficients in coronary heart disease: Table IV presents the standardized multivariate logistic regression coefficients for coronary heart disease and myocardial infarction in men aged 35 to 54 years. The regression analysis was performed with the independent variables—age, alcohol use, history of cigarette smoking, Metropolitan relative weight, systolic blood pressure, HDL and LDL cholesterol. Age, cigarette use, HDL and LDL cholesterol, all of which are significantly associated in the univariate case, retain their association with coronary heart disease when entered in a multivariate regression equation. From this same list of variables, only age and HDL cholesterol were significantly associated with myocardial infarction.

Frequency distribution of various lipoproteins: The frequency distribution of various lipoproteins in men 35 to 54 years old with and without coronary heart disease are presented in histograms. The distribution of LDL cholesterol in men with coronary disease showed a marked shift and 75 percent of this group had LDL cholesterol values that exceeded the mean LDL cholesterol value for the men without coronary disease (Fig. 1). There was little evidence for different variation in the two groups, and neither distribution showed dramatic skewness.

TABLE III

Mean Levels of Variables in Men With and Without Coronary Heart Disease (CHD): Framingham Male Offspring, Aged 35 to 54 Years

Variable	Men With CHD	Men Without CHD
Age (yr)	47.2‡	43.4
Total cholesterol (mg/dl)	229†	212
HDL cholesterol (mg/dl)	38.4†	44.3
LDL cholesterol (mg/dl)	158*	140
VLDL cholesterol (mg/dl)	33.9	28.0
Total cholesterol/HDL ratio	6.36‡	5.12
Alcohol (once/week)	5.5	6.2
Cigarette user	95%†	72%
Metropolitan relative weight	125	124
Blood pressure (systolic) (mm Hg)	133	128
Number§	38	1274

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; (two-sided *t* tests used. § Minimal number for which all variables were available.

TABLE IV

Standardized Multivariate Logistic Regression Coefficients for Coronary Heart Disease (CHD) and Myocardial Infarction (MI): Framingham Male Offspring, Aged 35 to 54 Years

Variable	Men With CHD (standardized coefficient)	Men With MI (standardized coefficient)
Age	0.683‡	0.700†
Alcohol	−0.099	0.136
Cigarettes	0.756*	0.453
Metropolitan relative weight	−0.050	−0.389
Blood pressure (systolic)	0.134	0.144
HDL cholesterol	−0.618†	−0.695†
LDL cholesterol	0.284*	0.275
Number of cases§	38	23

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; (two tailed *t* tests used). § Numbe with all variables available.

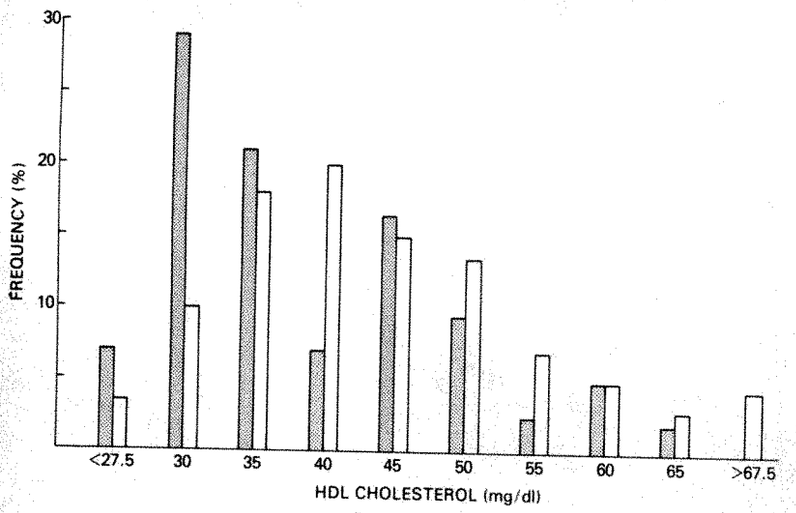


FIGURE 2. Frequency distributions of HDL cholesterol levels in men with (**stippled bars**) and without (**white bars**) coronary heart disease: Framingham male offspring aged 35 to 54 years.

Figure 2 shows the frequency distribution of HDL cholesterol in the men with and without coronary heart disease. Approximately 55 percent of the men with disease had a low value for HDL cholesterol (less than 35 mg/dl) and in none did the level exceed 68 mg/dl; in approximately 5 percent of the men without coronary disease the level exceeded this value.

The relative frequencies of various total cholesterol/HDL ratios in men with and without coronary heart disease are shown in Figure 3. The distribution of the ratio shows slight skewness toward higher value in men without coronary disease and a marked skewness to lower values in the men with disease. Approximately 65 percent of the men with coronary disease had a total cholesterol/HDL ratio greater than 5.5, compared with only 35 percent of the men without disease.

Table V summarizes the associations of high LDL cholesterol (more than 150 mg/dl) and low HDL cholesterol in men with and without coronary heart disease.

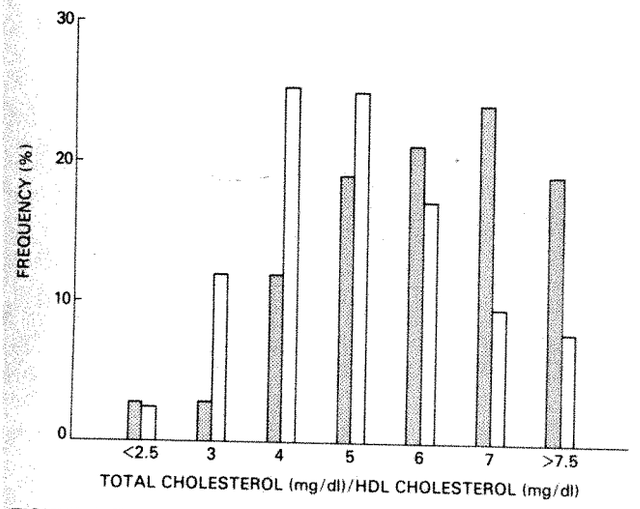


FIGURE 3. Frequency distributions of values for total cholesterol/HDL cholesterol ratio in men with (**stippled bars**) and without (**white bars**) coronary heart disease: Framingham male offspring aged 35–54 years.

In each instance, the men with disease are more likely to have these extreme values. High LDL and low HDL cholesterol in the same person was much more common among the men with disease.

Discussion

Prevalence of coronary heart disease in past 2 decades: This report demonstrates that coronary heart disease is still a highly prevalent disease in Framingham, Massachusetts. The original cohort was first seen in 1948 to 1951, and their offspring were examined from 1971 to 1975. Over that 20 year span the national mortality rates for coronary heart disease have escalated, peaked and declined since the late 1960's. Not enough is known about the trend in prevalence of coronary heart disease over the past 2 decades. Many of the published comparisons are based on health statistics, and comparability suffers because of changes in diagnostic methods and criteria as well as population shifts.[10]

Previous comparison of the cohort and offspring[11] has demonstrated striking reductions in cigarette smoking, and modest but statistically significant reductions in total plasma cholesterol levels. However, the Mantel-Haenszel analysis applied to 5 year age groups showed that the proportion of men with coronary heart disease was significantly greater among the offspring than in the cohort.

Recent publications have discussed the decline in coronary heart disease mortality, and investigators have queried whether that phenomenon stems from a decrease in case fatality, a decline in the incidence or some combination of these two effects.[10] The increased prevalence among the offspring supports the former contention, but such conclusions should be drawn with caution, especially when reductions in major risk factors that would be likely to decrease incidence are apparent. Previous analysis[11] showed that parents of children who did not participate in the offspring study were no different from the parents of those who did participate. However, it is possible that increased health awareness among men in the offspring generation led to a greater

participation among subjects with clinically recognizable coronary heart disease. Such a trend involving a small proportion of the sample would not be detectable when comparing parents of participants and nonparticipants.

Contribution of hyperlipoproteinemia to prevalence of coronary heart disease: Hyperlipoproteinemia, especially hyperbetalipoproteinemia, has been shown to contribute greatly to the frequency of coronary heart disease in young adults.[12] The contribution of hyperlipoproteinemia to coronary heart disease occurring in the 5th and 6th decades is also thought to be considerable.[13] In our study (Table II), approximately one third of the men and women with coronary heart disease and myocardial infarction had abnormal cholesterol or triglyceride levels as assessed with the Fredrickson criteria. Our results show that these classifications are associated with coronary heart disease, but they are not present within the majority of the group with coronary disease in this age range, as about two thirds of our men and women with coronary heart disease had "normal" lipoprotein cholesterol levels. Of course, offspring who have died of coronary heart disease are not included in this report. It is possible that those persons are more likely to have had such elevations of lipoprotein levels.

Our data (Table III) emphasize the importance of lipoprotein cholesterol quantification in showing an association between these variables and coronary heart disease in men less than age 54 years. Previously, total serum cholesterol was shown to be associated with coronary heart disease in subjects under age 50 years and to lose its predictive power in the older age groups.[14] Our data indicate significant univariate associations for HDL and LDL as well as total cholesterol. These results are similar to those of other studies in Israel,[1] Sweden,[15] Framingham,[16] and Honolulu,[17] and Evans County.[17]

Multivariate analysis of risk variables: Some of the variables that are highly associated with coronary heart disease in the univariate case lose their significance in the multivariate analysis. For the variables shown in Table IV, only age, history of cigarette use and HDL and LDL cholesterol levels retain their strength in contributing significantly to the association with coronary heart disease. A similar result is obtained when myocardial infarction replaces coronary heart disease as the dependent variable in the logistic equation. In this case, a previous history of smoking and LDL cholesterol are not significantly associated with coronary heart disease. However, the coefficients do remain positive. If the total cholesterol/HDL ratio is substituted for HDL and LDL cholesterol levels, and the other variables are retained, similar results are obtained and the total cholesterol/HDL ratio is significantly associated with coronary heart disease and myocardial infarction in the multivariate case. If VLDL cholesterol is added as an independent variable in this multiple regression, no significant independent role is demonstrable over and above the associations of HDL and LDL cholesterol levels. The association of the independent variables in Table IV and coronary heart disease is shown in Figure 4. The quintile of risk from the multivariate regression coefficients of Table IV is used to predict the actual number of cases of coronary heart disease.

TABLE V

Associations of Low HDL Cholesterols and High LDL Cholesterols With Coronary Heart Disease (CHD): Framingham Male Offspring, Aged 35 to 54 Years

	Men With CHD (n = 43)	Men Without CHD (n = 1267)
Low HDL cholesterol (<35 mg/dl)	20 (46%)	262 (21%)
High LDL cholesterol (<150 mg/dl)	23 (53%)	442 (35%)
High LDL cholesterol and low HDL cholesterol	9 (21%)	90 (7%)
Low LDL cholesterol and high HDL cholesterol	9 (21%)	653 (52%)

Significance of HDL decrease and VLDL cholesterol elevation: Because HDL and VLDL cholesterol show substantial negative correlation in these and other data,[18] it is possible that much of the association of VLDL cholesterol with coronary heart disease stems from the association of lower HDL cholesterol levels and coronary heart disease. When VLDL cholesterol replaced HDL cholesterol in a multiple regression, no significant association with coronary heart disease, independent of LDL cholesterol, cigarette smoking and age, was demonstrable. Thus, it appears that elevation of VLDL cholesterol and decrease in HDL cholesterol do not bear comparable information and thus have different implications for risk of coronary heart disease. However, in these data HDL cholesterol is more strongly associated with coronary heart disease than is VLDL cholesterol.

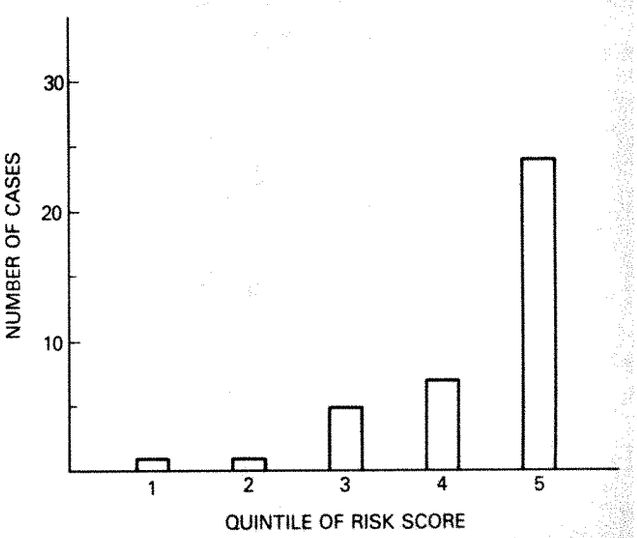


FIGURE 4. Prevalence of coronary heart disease by quintile of risk in men aged 35–54 years: Framingham Offspring Study. (Logistic regression coefficients using variables from Table IV were employed for the analysis.)

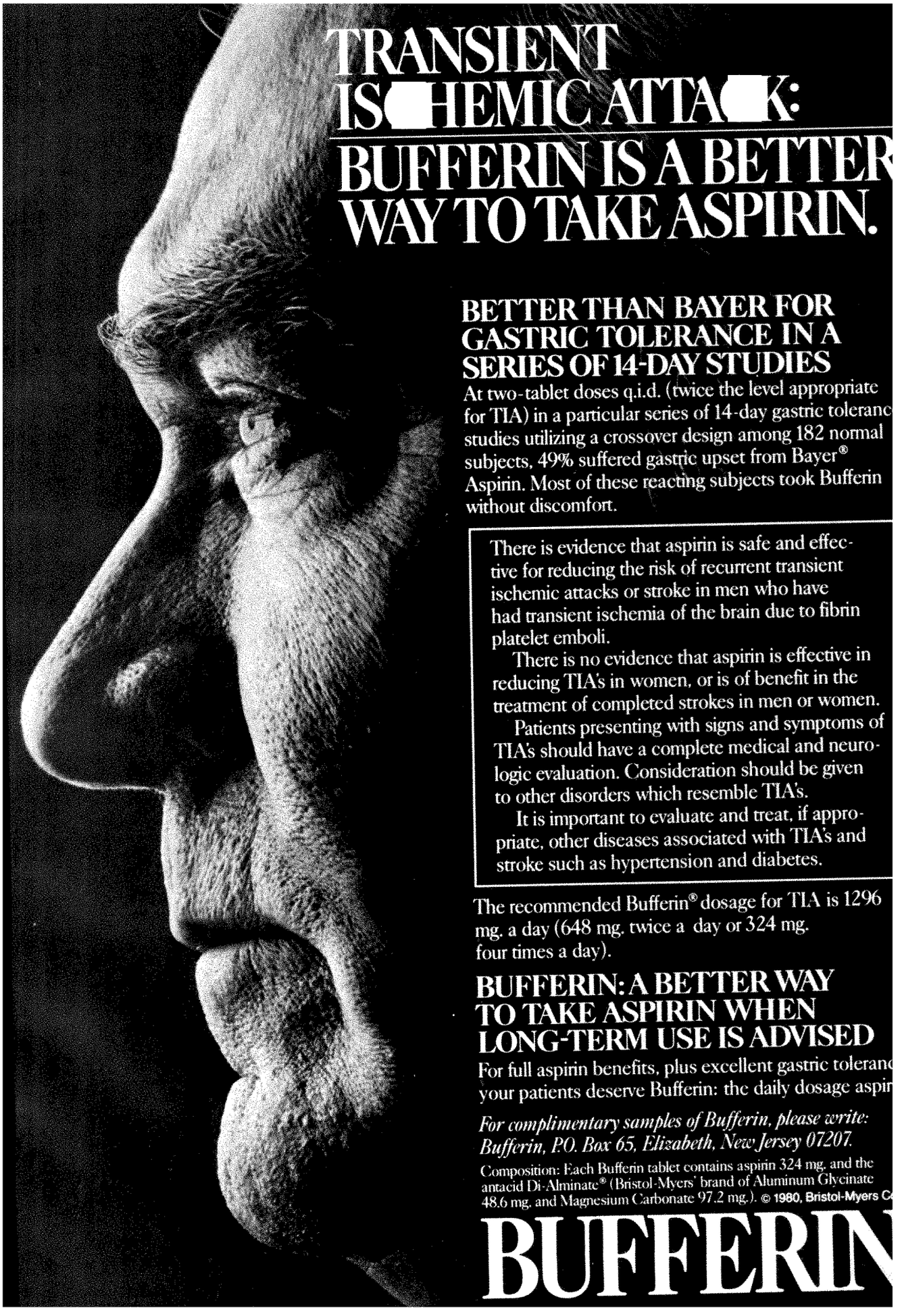
The failure to identify associations between coronary heart disease and alcohol consumption in our data should be considered cautiously. As with any data on alcohol consumption arising from personal interviews, there is suspicion of underreporting by some subjects. Given the strong relation between alcohol ingestion and HDL cholesterol,[6] it is possible that part of the association assigned by the analysis to HDL cholesterol may in fact derive from alcohol consumption, if the sample of subjects without coronary heart disease shows greater underreporting of alcohol consumption than the sample of subjects with coronary disease. Again, incidence data may add information on this subject.

Role of LDL versus HDL cholesterol: LDL and HDL cholesterol levels play important independent roles in the multiple logistic regression. Figures 1 and 2 give a visual presentation of the strengths of these associations. When either lipoprotein cholesterol was considered alone, there was no distinct separation between men with and without coronary heart disease. Total cholesterol/HDL ratio as a summary of lipoprotein quantification did not lead to an obvious separation of the two groups (Fig. 3). Furthermore, the interpretation of these data was subject to the severe limitations of prevalence data. First, any modification of life styles subsequent to the development of clinical disease might influence lipoprotein cholesterol concentrations[19-21] in a favorable manner and would have the effect of reducing the strength of association. Also, adverse lipoprotein profiles may be more likely to lead to fatal disease. Again, if this is true, the prevalence data would underestimate the true association of coronary heart disease and lipoprotein cholesterol levels.

Clinical implications: Other investigators have utilized lipoprotein summary statistics to show an association with coronary heart disease.[22] We obtained results similar to those for total cholesterol/HDL ratio when the LDL/HDL ratio was used. In an effort to give the clinician a useful index to associate lipid values with coronary disease, the total cholesterol/HDL ratio has been used. Total cholesterol is easily measured, and with improved techniques and quality control the same will probably hold for nonresearch HDL cholesterol determinations in the near future.[23]

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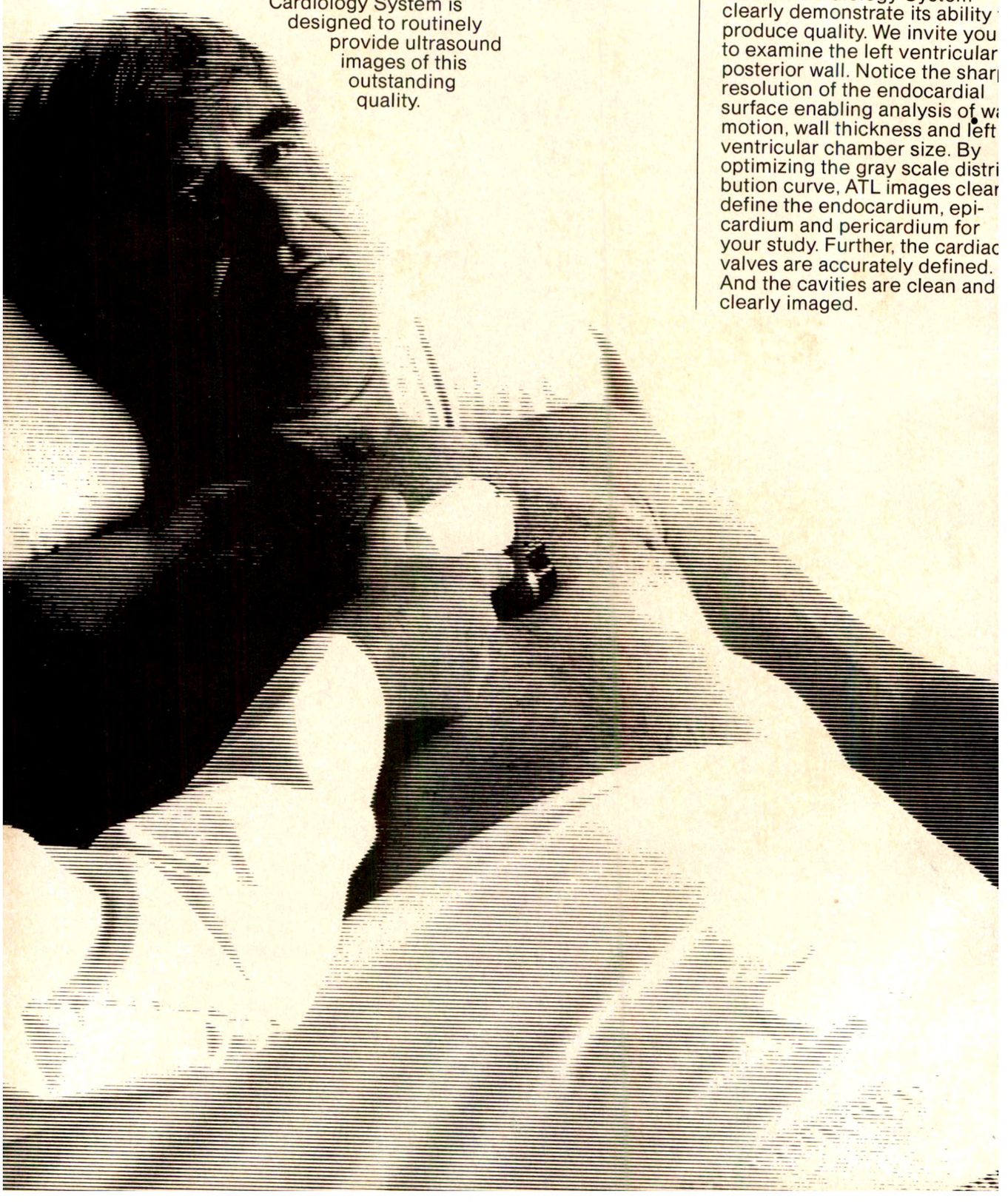
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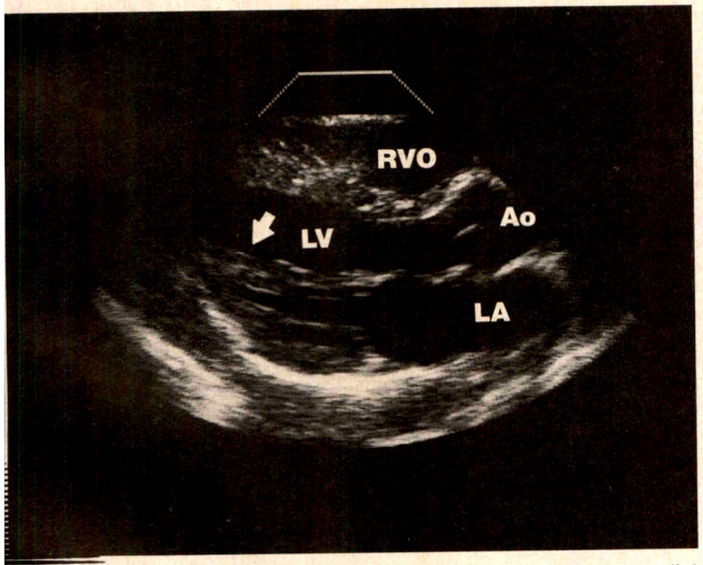
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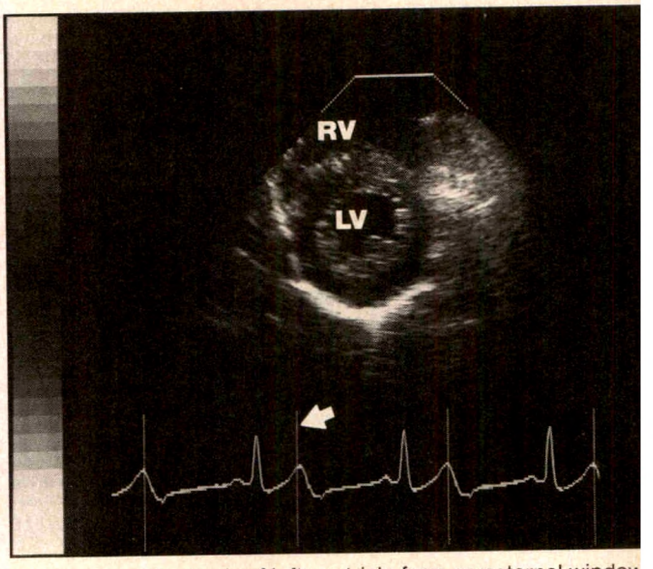


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Long axis view, parasternal window. Slight medial angulation reveals papillary muscles (arrow).

LV=left ventricle. RVO=right ventricular outflow. Ao=aorta. LA=left atrium.



Short axis of left ventricle from parasternal window cursor-triggered freeze f

LV=left ventricle. RV=right ver
Arrow=ECG

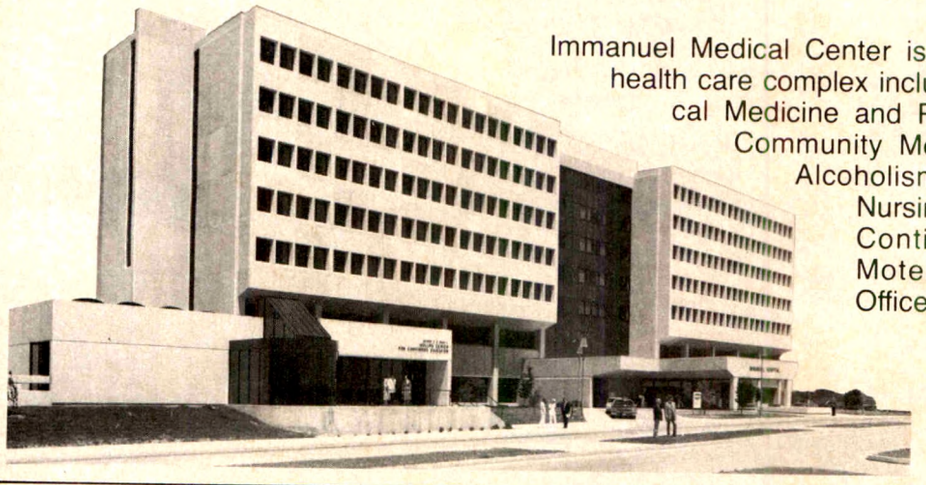
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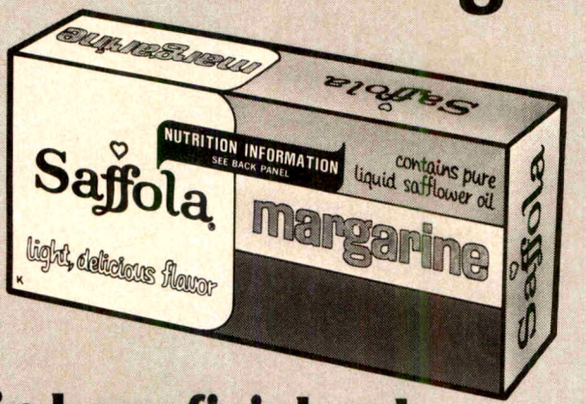
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Immanuel Medical Center is an all-new 615-bed health care complex including Hospital, Physical Medicine and Rehabilitation Center, Community Mental Health Center, Alcoholism Treatment Center, Nursing Home, Center for Continuing Education, Motel, and Physicians' Office Building.

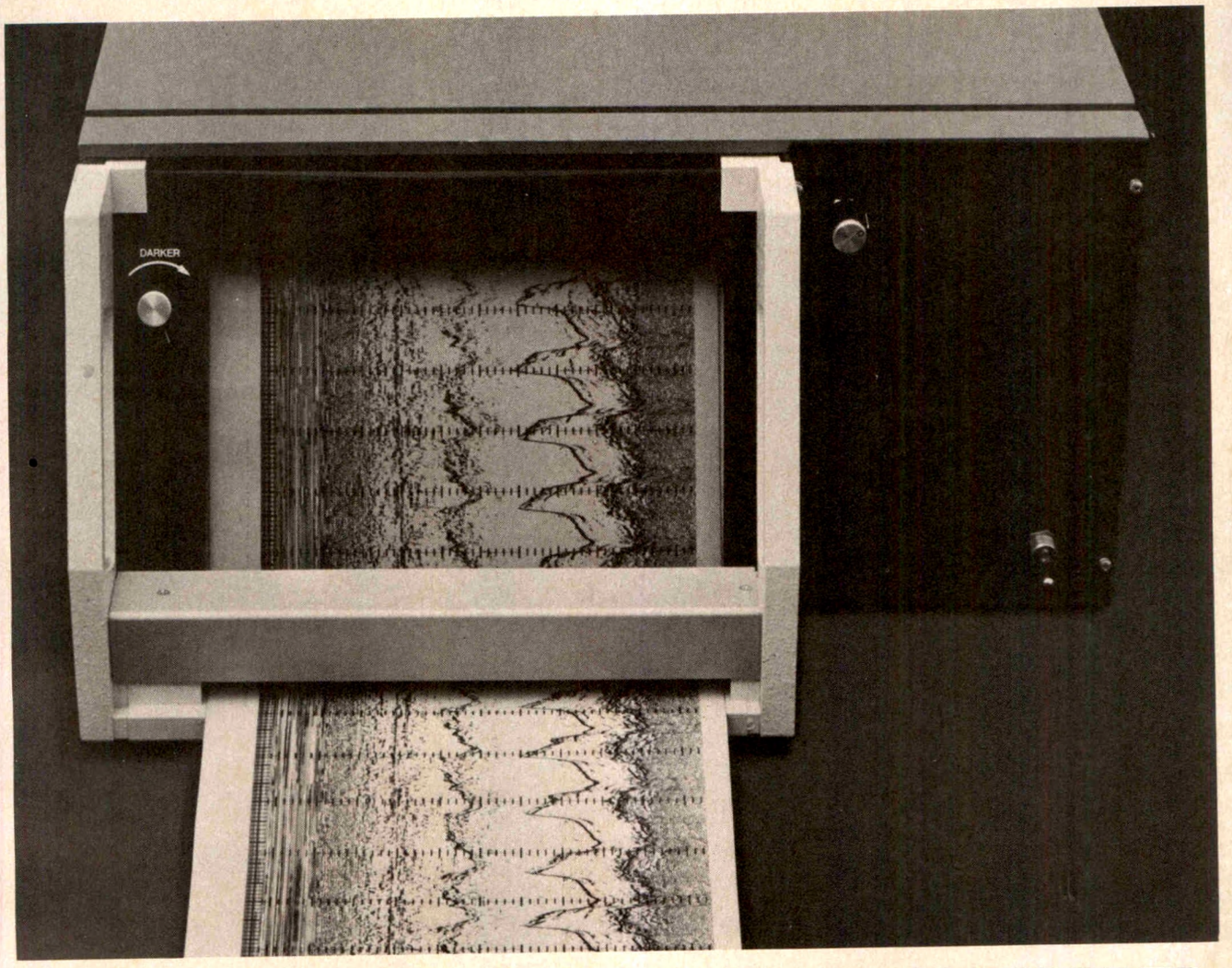
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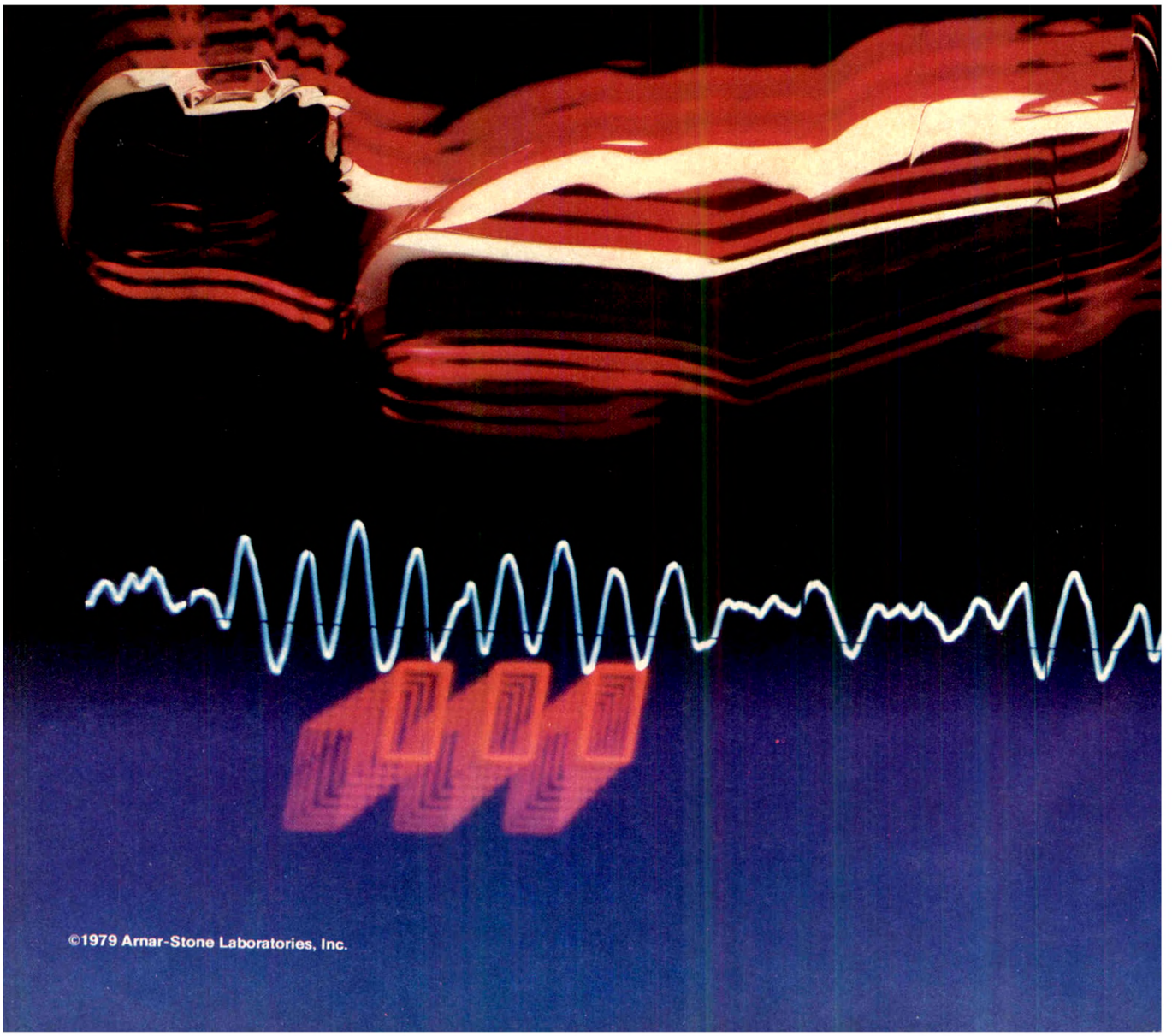
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BRETYLOL®
(bretylium tosylate)

Unique antifibrillatory-antiarrhythmic effect
Unique mechanism of action
Unique safety: no cardiac depression

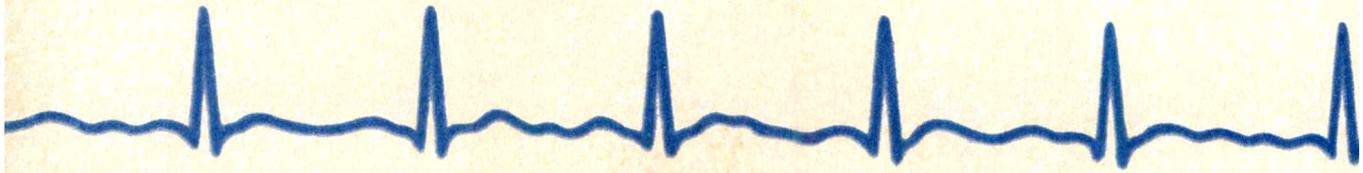




Bretylol® (bretylium tosylate), the unique new antifibrillatory-antiarrhythmic, provides lifesaving effects in the suppression of life-threatening ventricular arrhythmias unresponsive to lidocaine.

See last page of this advertisement for prescribing information.

BRETYLOL®
(bretylium tosylate):



Lifesaving potential in refractory ventricular arrhythmias

Unique antifibrillatory-antiarrhythmic effect

Studies in laboratory animals demonstrate that Bretylol significantly raises the ventricular fibrillation threshold with a consistency and magnitude that appears to be unique among antiarrhythmic agents.[1]

Bretylol (in conjunction with electrical cardioversion) frequently restores a normal sinus rhythm within minutes following intravenous injection in patients with ventricular fibrillation who have not responded to lidocaine.

Bretylol often controls ventricular tachycardia and other life-threatening ventricular ectopic rhythms, even when recurrent or refractory to lidocaine.

Clinically, Bretylol exhibits specific therapeutic effectiveness against refractory ventricular arrhythmias of various etiologies; for example, ventricular fibrillation and/or tachycardia associated with myocardial infarction,[2,6,9,10] open heart surgery,[7,8,10] and ischemic heart disease.[7] In one review of published experimental and clinical experiences with Bretylol,[11] the authors state, "clinical experience indicates that bretylium (Bretylol®) is frequently effective in the acute control of recurrent ventricular tachycardia or fibrillation resistant to other antiarrhythmic drugs... (and)...response of refractory ventricular arrhythmias to bretylium has been impressive."[11]

Unique safety

Unlike other antiarrhythmics, Bretylol does not depress cardiac function or exert a negative inotropic effect.[3]

There are no reports of Bretylol causing toxicity to any of the organs, including liver, kidney, heart, bone marrow, blood or central nervous system.

Therapy is generally well tolerated, and treatment is seldom discontinued because of adverse effects.

Reductions in blood pressure (usually orthostatic) may occur as a result of adrenergic blockade. If the patient is kept supine, the reduction in blood pressure is not usually clinically significant. Serious supine hypotension can occur in a few patients. Moreover, hypotension sometimes observed with Bretylol is not necessarily increased when the dosage is increased.

Unique cardiac effect

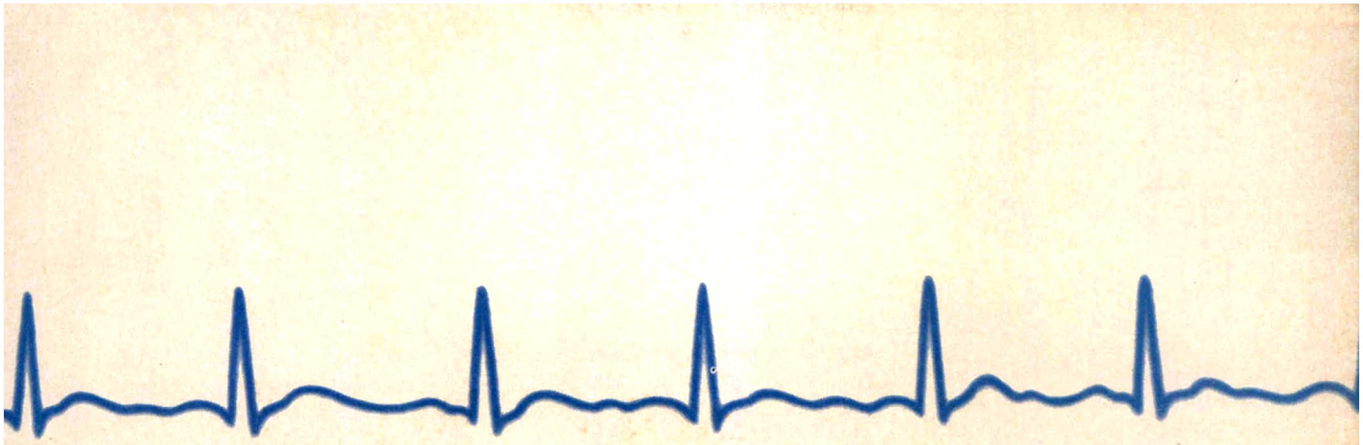
In laboratory studies Bretylol demonstrates a positive inotropic effect on the myocardium. Clinical reports confirm that Bretylol maintains cardiac output and does not depress myocardial function.[3]

Therefore, when used as an antiarrhythmic Bretylol should not interfere with the major therapeutic goal in the M.I. or post-open heart patient—the preservation of cardiac function.

It is recommended that the clinician consult the full prescribing information for dosage instructions and possible adverse effects prior to using Bretylol.

References:

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BRETYLOL® bretylium tosylate

Brief Summary of Prescribing Information

CLINICAL PHARMACOLOGY—BRETYLOL (bretylium tosylate) suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.
2. Increase in action potential duration and effective refractory period without changes in heart rate.
3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.
4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing reentry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS—BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS—There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS—Administration of BRETYLOL regularly results in postural hypotension. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses lower than those needed to suppress arrhythmias.

Patients should be kept in the supine position until tolerance to the hypotensive effect of BRETYLOL develops. Tolerance occurs unpredictably but may be present after several days.

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unless there are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of dopamine or norepinephrine may be used to raise blood pressure. When catecholamines are administered, a dilute solution should be employed and blood pressure monitored closely because the pressor effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or plasma and correction of dehydration should be carried out where appropriate.

Due to the initial release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, transient hypertension or increased frequency of premature ventricular contractions and other arrhythmias may occur in some patients.

The initial release of norepinephrine caused by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia occurs in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia does not appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simultaneous initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

In patients with fixed cardiac output (i.e., severe aortic stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hypotension may result from a fall in peripheral resistance without a compensatory increase in cardiac output. If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive catecholamines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY—The safety of BRETYLOL in human pregnancy has not been established.

USE IN CHILDREN—The safety and efficacy of this drug in children has not been established.

PRECAUTIONS—BRETYLOL should be diluted (one part BRETYLOL with four parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous use. Rapid intravenous administration may cause severe nausea and vomiting. Therefore, the diluted solution should be infused over a period greater than 8 minutes. In treating existing ventricular fibrillation BRETYLOL should be given as rapidly as possible and may be given without dilution.

When injected intramuscularly, not more than 5 ml should be given in a site, and injection sites should be varied since repeated intramuscular injection into the same site may cause atrophy and necrosis of muscle tissue, fibrosis, vascular degeneration and inflammatory changes.

Since BRETYLOL is excreted principally via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS—Hypotension and postural hypotension have been the most frequently reported adverse reactions. Nausea and vomiting occurred in about three percent of patients, primarily when BRETYLOL was administered rapidly by the intravenous route. Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postural hypotension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hypertension, initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, and sensation of substernal pressure have also been reported in a small number of patients, i.e., approximately 1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash, flushing, hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized tenderness, anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have been reported in about 1 patient in 1000. The relationship of BRETYLOL administration to these reactions has not been clearly established.

HOW SUPPLIED—NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injection, USP.

January 1980

Please refer to complete prescribing information prior to use.

American Critical Care
(formerly Arnar-Stone Laboratories)
Division of
American Hospital Supply Corporation
McGaw Park IL 60085

The Sell-Out Syndrome

'Never' is a long time and so that word probably shouldn't be used. But I'm tempted to say it in the face of so many other medical electronic firms selling out all around us. I cannot believe that money really means that much.

In 1965 I started Marquette Electronics in a funny old building that had 1600 square feet of space. I invested $7,500 and my partner another $7,500. Life was an unbelievable struggle. Designs didn't work, the customer didn't pay, the money ran short, and I worked fifteen hours a day. My partner continued with another business we had so we could both eat.

Today Marquette is $22 million in sales, 100,000 square feet of modern manufacturing facilities, some of the best researchers in the business, and world leadership in electrocardiography.

Every week someone contacts me to ask if we would sell out, be acquired, merge or otherwise mess up our beautiful world of success. People suggest absolutely wild prices, unbelievable benefits, and infer that if we won't budge, we'll be destroyed by the 'giants'.

Every month some company like ours is sold for those fancy prices to some overly profitable giant, and everyday I hear of the horrors from the guys who stick around for the bureaucratic onslaught. Everyday I hear how the good old Yankee entrepreneurial spirit is broken into millions of pieces by a conglomerate without spirit, heart or even an ability to get things done.

Of course there are special circumstances that might necessitate a sell-out. The key guy dies. Some bad luck drains the financial resources dry. A competitor strikes a tough blow or the government legislates you to your knees. And, yes, I know I can't be the chief executive forever, but does that mean we must sell out and destroy what we have struggled to build over the most productive years of our lives?

These would be buyers tell me we need more money to keep up with research. Hog wash! I can't pump money into our Engineering Department of brilliant guys to make them invent or develop faster. We always seem to be ahead of our competition in innovation anyway, so how can more money make it happen better or faster?

They say we'll need money for continued growth. But our profits provide for our growth, and we grow 25-35% a year and make sure to stay profitable so our bankers loan us the needed operating capital. They said we'd need money for new facilities, yet our beautiful 100,000 square foot plant was entirely financed by an industrial bond issue.

So what, then, are the alternatives? Just keep growing and going forever? We all get old in the end and we must make room for the young if we wish to perpetuate our company and what it stands for. If we have kids that want to step in, that's fine, but they have to want to and they have to be every bit as talented and ambitious as anyone else.

Our government has worked hard for many years to make the transfer of ownership in a company like ours to our young talent almost impossible. They have set capital gain taxes, gift taxes, income taxes and miscellaneous taxes of all kinds such that it's easy to go broke or go to jail if you ever get such a dumb idea, but we're going to try anyway. We're going to set our course for the next ten years so that we let the young, talented, capable guys in our company become major stockholders. And the stock will come from us...the old timers who must step back and have faith that someone else can carry on the work we're doing to advance the science of electrocardiography.

Someday I may regret writing these words. Someday I may wish we didn't turn our backs on those big, juicy offer from the conglomerates, but I don't think so. And in these words may be a lesson to others about what made this country and its industry great in the first place — and it surely wasn't going part way and then selling out to a devouring giant for the sake of money.

Sincerely,
Michael J. Cudahy
President

marquette electronics inc.
Milwaukee, WI, USA

Vagal Techniques for Termination of Paroxysmal Supraventricular Tachycardia

MENASHE B. WAXMAN, MD
ROBERT W. WALD, MD
ARJUN D. SHARMA, MD
FELIX HUERTA, MD
DOUGLAS A. CAMERON, MD

Toronto, Ontario, Canada

Maneuvers that reflexly increase vagal tone were deployed to terminate the tachycardia in 68 consecutive patients with paroxysmal supraventricular tachycardia. The order and success rate of the protocol was as follows: 57 episodes were terminated with carotid sinus pressure alone or after pretreatment with edrophonium, 5 were terminated with the Valsalva maneuvers and 6 were terminated with phenylephrine. Potency testing showed that phenylephrine evoked the greatest increase in vagal tone. All cases demonstrated slowing of tachycardia ranging from 40 to 220 ms ± standard error of the mean (mean 79.0 ± 3.8 ms) followed by abrupt termination. Pauses after termination ranged from 900 to 3,300 ms (mean 1,683.8 ± 66.6) with 54 patients showing pauses of 2,000 ms or less. Termination was highly reproducible showing an overall success of 148 (92 percent) of 160 trials among 22 selected cases. The extent of increased vagal tone needed to terminate paroxysmal supraventricular tachycardia was raised by augmented sympathetic tone (infusion of isoproterenol) and decreased by reduced sympathetic tone (pretreatment with propranolol). Thus, paroxysmal supraventricular tachycardia can be rapidly, safely and consistently terminated by maneuvers that reflexly increase vagal tone.

Maneuvers that increase vagal tone have been used to terminate paroxysmal supraventricular tachycardia since at least 1913 and have gained wide acceptance.[1–14] Termination of tachycardia by an increase in vagal tone not only is immediate but also may be a specific test for paroxysmal supraventricular tachycardia[1,4,15] In contrast, other supraventricular tachycardias such as sinus or ectopic atrial tachycardia, atrial flutter or atrial fibrillation usually show transient slowing of the ventricular rate, whereas ventricular tachycardia with rare exceptions shows no response to increased cardiac vagal tone.[4,7,15–17] In this study we report our experience in terminating 68 consecutive cases of paroxysmal supraventricular tachycardia by a select group of maneuvers that reflexly enhance vagal tone

This study was performed with several objectives in mind: (1) to establish prospectively the success rate with which a fixed protocol of common vagal maneuvers terminates paroxysmal supraventricular tachycardia; (2) to assess the reproducibility of various vagal maneuvers to terminate such tachycardia; (3) to measure the relative potency of different vagal techniques to terminate such tachycardia; (4) to examine the behavior of such tachycardia preceding its termination with vagal maneuvers; (5) to establish the safety of these interventions; and (6) to measure the effects of altered sympathetic activity on the potency of the vagal maneuvers used to terminate the tachycardia.

From the Department of Medicine, University of Toronto Faculty of Medicine and Division of Cardiology of the Toronto General Hospital, Toronto, Ontario, Canada, This work was supported in part by grants from the Ontario Heart Foundation, Toronto and the Canadian Heart Foundation, Ottawa, Ontario, Canada. Manuscript received December 18, 1979; revised manuscript received March 3, 1980, accepted April 10, 1980.

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Methods

Study Patients

Sixty-eight consecutive patients with recurrent paroxysmal supraventricular tachycardia were studied during spontaneous or induced episodes of tachycardia at the Toronto General Hospital between 1972 and 1976. The patients ranged in age from 14 to 74 (mean 42) years. The clinical cardiac diagnosis in the 68 patients was no cardiac disease (51 patients,) coronary artery disease (5), rheumatic valve disease (6), mitral valve prolapse (3) and Ebstein's anomaly of the tricuspid valve (3). Thirty-three patients (group A) were seen in the Emergency Department with established paroxysmal supraventricular tachycardia because the attending physicians there were unable to terminate the arrhythmia by maneuvers that increased vagal tone. In these patients there was generally only one opportunity to terminate the tachycardia unless a second episode started spontaneously. Of these patients, two were receiving oral digoxin (0.25 mg daily), three were receiving propranolol (40 to 160 mg daily) and one was receiving quinidine sulfate (800 mg daily). Thirty-five patients (group B) were referred electively for electrophysiologic studies because they had had for many years recurrent long-lasting attacks that posed diagnostic and therapeutic problems. In these patients all drugs were discontinued at least 3 days before the studies. During electrophysiologic studies multiple episodes of paroxysmal supraventricular tachycardia were induced and terminated.

Features of the tachycardia: In all patients the features of the tachycardia met criteria that suggested it involved or was confined to the atrioventricular (A-V) node.[18–22] The characteristics of the attacks were: (1) sudden onset and sudden offset; (2) the QRS configuration during the tachycardia was identical to that during sinus rhythm except for cases with rate-related aberration or cases with overt Wolff-Parkinson-White preexcitation syndrome. In the latter group the QRS configuration during tachycardia was either normalized and identical to His bundle escape beats or aberrant in a rate-related manner[15,23,24]; (3) the heart rate ranged from 140 to 220 beats/min; (4) the atria and ventricles were always fixed in a 1:1 ratio; and (5) surface P waves either were not seen because they were inscribed simultaneously with the QRS complexes or, when seen, were confined to the proximal portion of the S-T segment.

Patients in group B (35 cases) underwent electrophysiologic studies and the following additional criteria suggested that the A-V node participated in the tachycardia: (1) the attacks could easily be initiated by single early premature atrial stimuli that conducted with a critically prolonged A-V nodal conduction time[25]; (2) attacks could be terminated by a single well timed atrial stimulus[25,26]; (3) atrial electrograms showed that atrial depolarization in all cases occurred either coincident with the QRS complex or within the proximal portions of the S-T segment and the direction of depolarization was always retrograde[21,27–30]; and (4) a His bundle potential preceded the QRS complexes with an H-V interval range of 40 to 55 ms.

These cases could be further subdivided into those that involved an overt or concealed lateral accessory A-V pathway and those that did not.[20,28] Participation of a lateral accessory A-V pathway (overt or concealed) in the tachycardia circuit was based on the following two criteria: (1) Eccentric retrograde atrial activation sequence followed each QRS complex during tachycardia,[29,30] and (2) spontaneous disappearance of functional bundle branch block during the tachycardia was accompanied by simultaneous acceleration of the tachycardia that was traceable to a reduced ventriculoatrial interval.[31–33] Of the 35 patients in group B, the tachycardia circuit was confined to the A-V node in 12 and involved a bypass tract in 23.

Study Protocols Pertinent to all Patients

Order of vagal maneuvers: In all 68 patients termination of tachycardia was attempted by one of us (M.B.W.) in the following consistent order: (1) single applications of left or right carotid sinus pressure; (2) multiple applications of unilateral carotid sinus pressure; (3) carotid sinus pressure after pretreatment with the anticholinesterase edrophonium hydrochloride (Tensilon®), 5 to 10 mg intravenously; (4) Valsalva maneuver; (5) Valsalva maneuver after pretreatment with edrophonium, 5 to 10 mg intravenously; and (6) phenylephrine, 0.1 to 1.0 mg intravenously. In each case the protocol was pursued until the tachycardia was terminated. This meant that the different methods were not tried with equal frequency during the performance of the initial protocol. For example, carotid sinus pressure was tried in all 68 patients whereas phenylephrine, the last intervention in the sequence, was tried in only 6 patients after all previous maneuvers had failed. In all subsequent studies the patients were categorized by the vagal maneuver that first terminated the tachycardia during this initial protocol.

The interval between the last QRS complex of the tachycardia and the first subsequent sinus conducted complex was measured to the nearest 50 ms interval. When several terminations were performed in a particular patient, the arithmetic mean of the pauses was used. Slowing of tachycardia before termination was determined by measuring the prolongation in cycle length from the control value to the last cycle of the tachycardia to the nearest 10 ms using high speed or magnified tracings. When several terminations were analyzed in the same patient, the arithmetic mean of these determinations was used.

Techniques of vagal maneuvers: In all patients, carotid sinus pressure was applied in a standard manner.[1,34] With the patient supine and the head hyperextended, the sinus (right or left) was compressed for 1 to 5 seconds using steady pressure rather than massage because the former is more reproducible in our hands. Valsalva maneuvers in patients in group A were not quantitated and consisted of a maximal strain held for 10 seconds. During Valsalva maneuvers performed by patients in group B, oral pressure was displayed on a manometer in full view of the patient, who was asked to maintain a constant pressure of 30 to 60 mm Hg for 5 to 10 seconds.[35] To prevent the patient from closing the glottis and generating oral pressure only, a small leak was introduced into the system. This obliged the patient to keep the glottis open during the strain phase, thus equilibrating intrathoracic and oral pressures.[35] Edrophonium hydrochloride, 5 or 10 mg, was administered as an intravenous bolus dose and either carotid sinus pressure or a Valsalva maneuver was performed 30 seconds later, at a time when the patient subjectively experienced some of the muscarinic and nicotinic actions of this drug.[5] Phenylephrine was administered as repeated intravenous bolus injections starting with 0.1 mg and increasing this dose in increments of 0.1 to 0.2 mg. The maximal dose administered was limited by the peak systolic pressure not being allowed to exceed 180 mm Hg. Blood pressure was measured at 15 second intervals in patients in group A and continuously in group B patients using an intraarterial line. After each dose of phenylephrine sufficient time was allowed to elapse for the blood pressure to return to the control value before the subsequent dose was administered.

Study Protocols in Patients in Group B

Electrophysiologic studies: The 35 patients in group B underwent intracardiac electrophysiologic studies. His bundle electrograms, high and low right atrial electrograms and low left atrial electrograms (recorded either from a catheter introduced into the left atrium through a probe-patent foramen ovale or from the distal coronary sinus) were monitored. The sequence of atrial activation was determined during the tachycardia and compared with that during sinus rhythm.[28–30] The right atrium was paced using right atrial pacing electrodes. Paroxysms of supraventricular tachycardia were initiated by scanning the entire diastole at intervals of 5 to 10 ms first with a single, then (if necessary) with multiple atrial stimuli.[36] Once supraventricular tachycardia was induced it was allowed to stabilize for 5 minutes, and at this point the protocol for termination was begun. During these studies the surface electrocardiogram, beat to beat heart rate, intraarterial blood pressure and oral pressure generated during the Valsalva maneuver were continuously recorded.

Reproducibility studies: To study the reproducibility of tachycardia termination with each vagal intervention, numerous episodes were induced in 22 selected patients. The following protocols were carried out: (1) single applications of carotid sinus pressure to terminate 10 episodes of paroxysmal supraventricular tachycardia in each of 10 patients (100 trials); (2) single applications of carotid sinus pressure to terminate 5 episodes of tachycardia in each of 5 patients after pretreatment with edrophonium hydrochloride, 10 mg intravenously (25 trials); (3) Valsalva maneuvers (40 mm Hg strain for 10 seconds) to terminate 5 episodes of tachycardia in each of 3 patients (15 trials); and (4) phenylephrine (minimal dose) to terminate 5 episodes of tachycardia in each of 4 patients (20 trials). Whenever a given episode failed to terminate with a particular intervention, the intervention was counted as a failure and the tachycardia was terminated with atrial pacing. In the patients undergoing these trials the tachycardia had originally been converted with the intervention being tried.

Potency studies: The relative potency of different vagal maneuvers was determined by finding and comparing the minimal dose of phenylephrine and corresponding pressor effect needed to terminate paroxysmal supraventricular tachycardia in (1) 15 patients whose tachycardia terminated with a single application of carotid sinus pressure; (2) 9 patients whose tachycardia terminated with carotid sinus pressure after administration of edrophonium; (3) 3 patients whose tachycardia terminated with a Valsalva maneuver; and (4) 4 patients whose tachycardia terminated only after administration of phenylephrine.

Effects of background sympathetic activity: Eight patients from group B were examined under various conditions of sympathetic activity. Four patients who responded to carotid sinus pressure and four who responded only to phenylephrine were selected. In the first four the rate of the tachycardia and the minimal dose of edrophonium needed to terminate it was determined during control conditions and after attainment of a new steady state with an isoproterenol infusion (2 μg/min intravenously). Edrophonium, used because it is a relatively pure vagal stimulant,[5,6] was administered as intravenous bolus injections in sequentially increasing doses of 5, 10, 15 and 20 mg until the tachycardia terminated. Sufficient time was allowed between consecutive doses to allow the heart rate to return to the control level and any subjective symptoms to disappear. In the four patients who required phenylephrine for termination of tachycardia, the minimal dose of phenylephrine required to terminate supraventricular tachycardia before and 10 minutes after partial beta adrenergic blockade with propranolol (0.07 mg/kg intravenously) was determined.

Effects of parasympathetic blockade: Eight other patients from group B were examined before and after partial vagal blockade with atropine, 1.2 mg intravenously. Four of these patients were from among those whose tachycardia terminated with carotid sinus pressure, two had responded to a Valsalva maneuver and two to phenylephrine. Termination of tachycardia by these maneuvers was documented and then retested 5 minutes after administration of atropine, 1.2 mg intravenously.

The purpose and methods of study were carefully explained and verbal and written consent were obtained from each participant.

Results

Overall response: The success rate of the various vagal maneuvers in terminating paroxysmal supraventricular tachycardia is shown in Figure 1. Tachycardias in all 68 patients could be terminated by the protocol. Among the 68 patients, the tachycardia responded to a single application of carotid sinus pressure in 25 and to multiple applications of carotid sinus

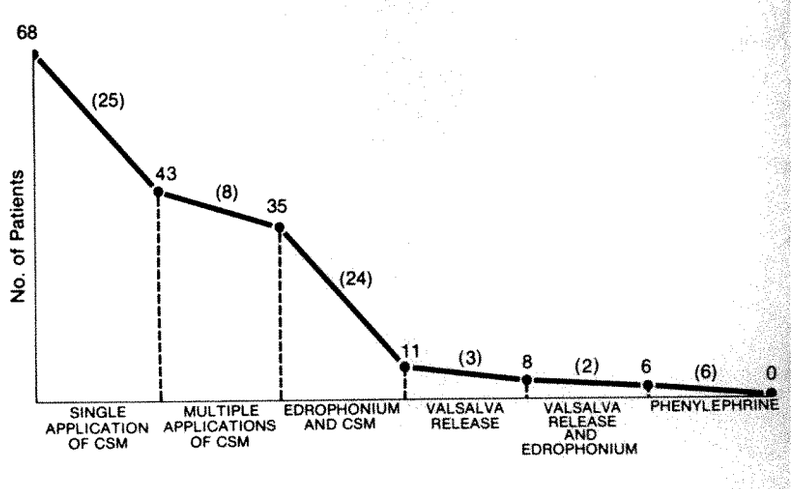


FIGURE 1. Success rate of termination of paroxysmal supraventricular tachycardia by different vagal maneuvers. The order of interventions along the abscissa corresponds to the protocol followed. The initial figure represents the number of patients submitted to any particular maneuver, and the figure in parentheses denotes the number whose tachycardia was terminated by each respective maneuver. For example, in 25 of 68 patients, tachycardia was terminated by a single application of carotid sinus massage (CSM) or pressure. In 57 of the 68, the tachycardia was terminated by single or multiple applications of carotid sinus pressure with or without edrophonium. In 5 of 11 patients the tachycardia responded to a Valsalva maneuver with or without edrophonium. In six of six patients the tachycardia was terminated with phenylephrine.

pressure in an additional 8. Among the remaining 35 patients, 24 episodes of tachycardia were terminated by carotid sinus pressure applied after pretreatment with edrophonium, 5 to 10 mg. Thus, in 57 of 68 patients, paroxysmal supraventricular tachycardia was terminated by carotid sinus pressure with or without injection of edrophonium. Carotid sinus pressure caused a decrease in arterial blood pressure that provided a semiquantitative measure of the extent and duration of the application.[37–39] After edrophonium, the extent of carotid sinus pressure needed to terminate paroxysmal supraventricular tachycardia as judged by the degree and duration of decrease in blood pressure was considerably less than that during the original application of carotid sinus pressure that failed to terminate the tachycardia (Fig. 2).

Among the remaining 11 patients who did not respond to carotid sinus pressure, the tachycardia was terminated by Valsalva maneuvers in 5 patients several seconds after release of the strain and coincident with the hypertensive phase (Fig. 3). Three of the six patients whose tachycardia could not be terminated by a Valsalva maneuver were in group A, and we were thus unable to determine the reason for failure; the other three patients could not maintain a strain above 22 mm Hg and thus an insufficient overshoot in blood pressure was produced. Phenylephrine in doses ranging from 0.1 to 0.6 mg terminated paroxysmal supraventricular tachycardia in all six remaining patients (Fig. 4).

Reproducibility of termination of paroxysmal supraventricular tachycardia: Once a specific vagal maneuver was found to terminate paroxysmal supraventricular tachycardia successfully in a particular patient, this observation was subsequently demonstrated to be highly reproducible. A single application of carotid sinus pressure terminated 92 (92 percent) of 100 episodes of tachycardia in 10 patients; 24 (96 percent) of 25 episodes after pretreatment with edrophonium in 5 patients; a Valsalva maneuver terminated 12 (80 percent) of 15 episodes in 3 patients; and phenylephrine terminated 20 (100 percent) of 20 episodes of in 4 patients. The overall success rate was 147 (92 percent) of 160 trials.

Relative potency of different vagal techniques: Use of the amount of phenylephrine and the pressor response as a measure of the degree of vagal stimulation required to terminate the tachycardia revealed significant differences among the various patient groups identified with the initial protocol (Fig. 5). Fifteen patients who originally responded to a single application of carotid sinus pressure required a mean dose of phenylephrine of 0.15 ± 0.02 mg to terminate their tachycardia; nine patients whose tachycardia terminated with carotid sinus pressure and edrophonium required a mean dose of 0.26 ± 0.02 mg of phenylephrine; three who responded to a Valsalva maneuver required a mean dose of 0.42 ± 0.04 mg of phenylephrine; and four who responded only to phenylephrine required an average dose of 0.50 ± 0.07 mg of the drug to stop the tachycardia. The corresponding average pressor responses were 16.8 ± 0.7, 26.1 ± 1.7, 36.7 ± 1.7 and 56.3 ± 5.0 mm Hg, respectively.

Behavior of paroxysmal supraventricular tachycardia before termination: In all patients, paroxysmal supraventricular tachycardia always exhibited some slowing before termination and then

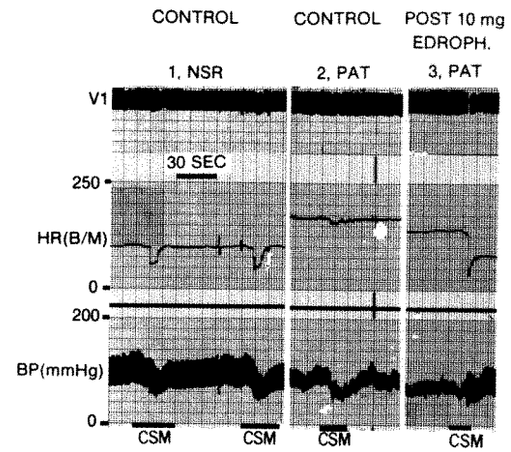


FIGURE 2. Case 1. Lead V_1, beat to beat heart rate (HR) in beats/min (B/M) and blood pressure (BP) in mm Hg, recorded during normal sinus rhythm (NSR) (**left panel**) and during supraventricular tachycardia (PAT) (**middle** and **right panels**). The extent and duration of carotid sinus massage (CSM) or pressure in each panel could be assessed semiquantitatively by the degree of reduction in blood pressure. During sinus rhythm, carotid sinus pressure decreased blood pressure and transiently slowed the rate of tachycardia. During control conditions, supraventricular tachycardia (**middle panel**) was not terminated with carotid sinus pressure alone. A vigorous application of carotid sinus pressure decreased blood pressure considerably and transiently slowed, but did not end, the tachycardia. After pretreatment with 10 mg of edrophonium (EDROPH) (**right panel**), the rate of tachycardia was slower. A smaller application of carotid sinus pressure again lowered blood pressure, slowed the tachycardia and restored sinus rhythm.

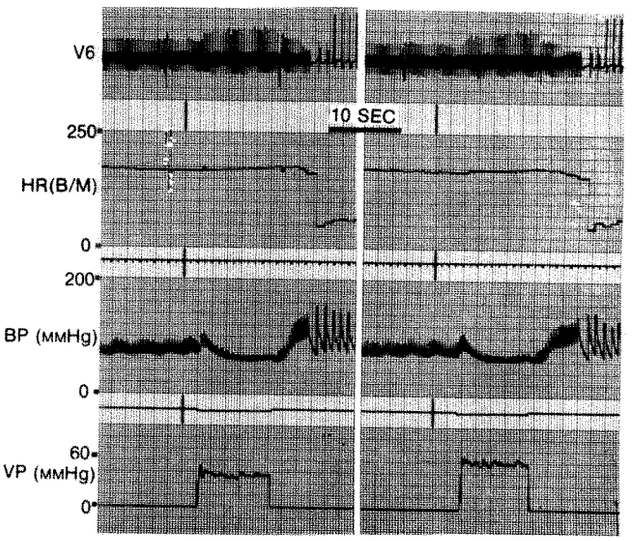


FIGURE 3. Case 2. Lead V_6, beat to beat heart rate (HR), blood pressure (BP) and Valsalva pressure (VP) recorded during two consecutive episodes of supraventricular tachycardia. The **left** and **right** panels show Valsalva pressures of 40 and 60 mm Hg, respectively. During the strain the peak and pulse pressure decreased. Several seconds after release of the strain, blood pressure rose above control level, the tachycardia slowed and then terminated.

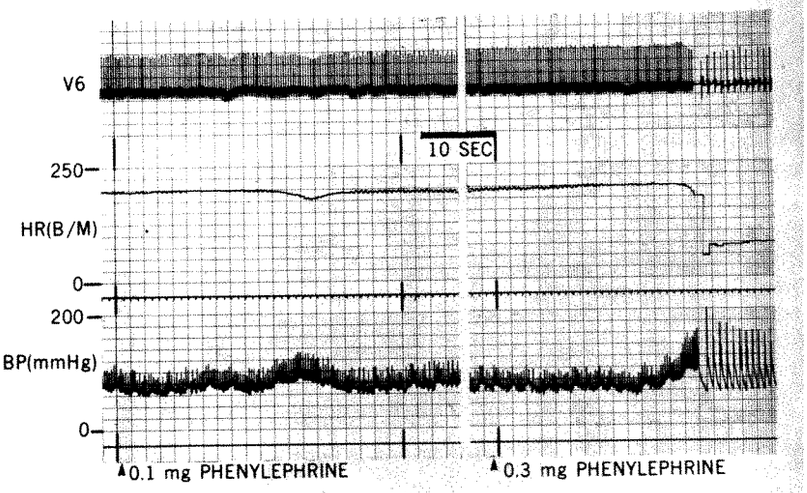


FIGURE 4. Case 3. Recordings of lead V_6, beat to beat heart rate (HR) and blood pressure (BP) during an episode of supraventricular tachycardia. **Left panel,** after administration of 0.1 mg of phenylephrine, the blood pressure increased and the tachycardia slowed transiently but did not terminate. **Right panel,** after administration of 0.3 mg of phenylephrine, the blood pressure was sufficiently increased to slow and stop the tachycardia.

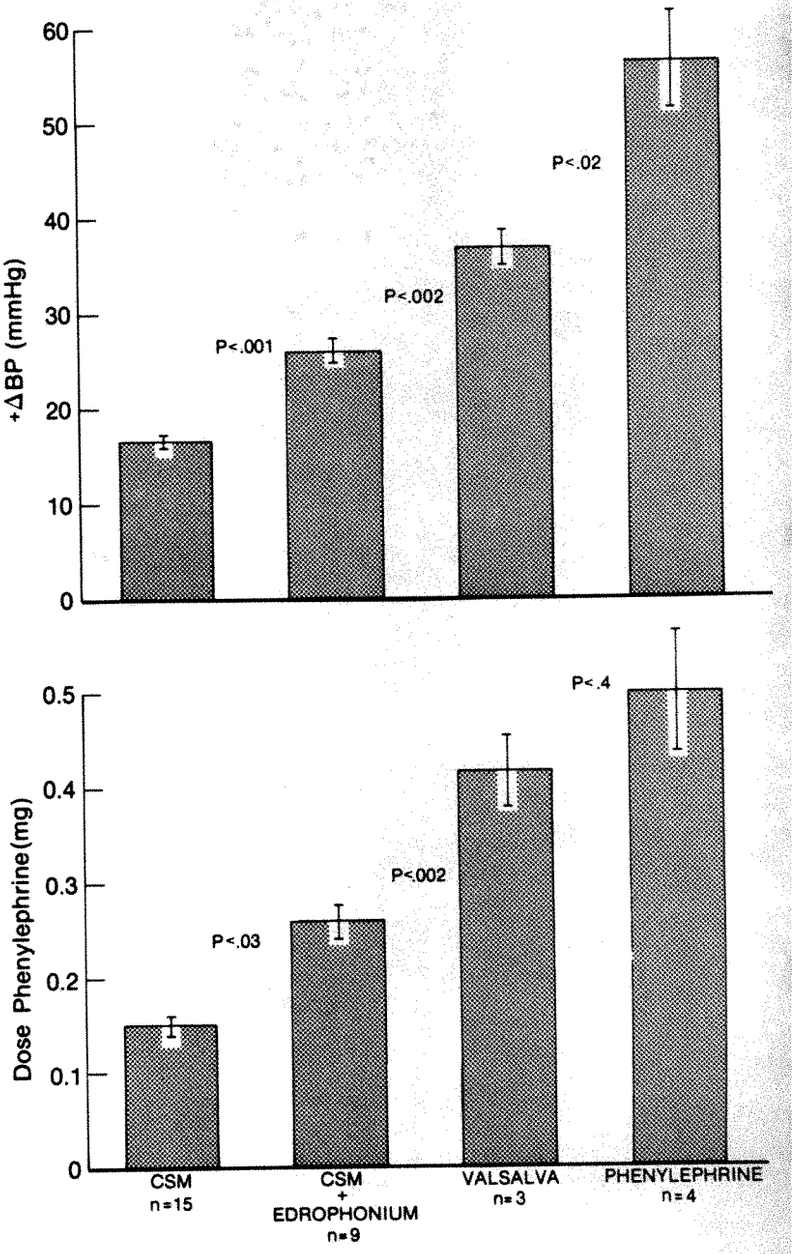


FIGURE 5. Comparison of the dose of phenylephrine and pressure response needed to terminate paroxysmal supraventricular tachycardia among the different patient groups. Patients who responded to a single application of carotid sinus massage (CSM) (pressure) required the smallest dose of phenylephrine for termination; those in the phenylephrine group required the largest dose and pressor response. Unlike the pressor difference between the Valsalva and phenylephrine groups, the difference in dose of phenylephrine in the two groups was not statistically significant. n = numbers of patients; p = probability.

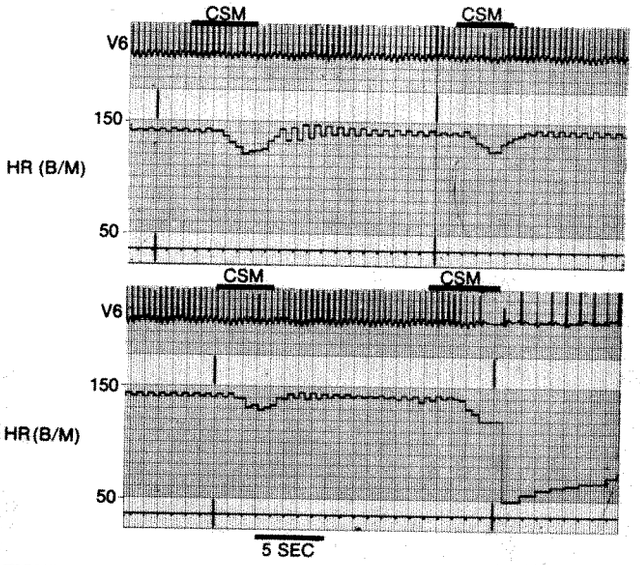


FIGURE 6. Case 4. Lead V_6 and beat to beat heart rate (HR) recorded during an episode of supraventricular tachycardia. Four applications of carotid sinus massage (CSM) (pressure) are shown. The first three applications produced slowing without termination and the tachycardia resumed its control rate in several seconds. The fourth application finally terminated the tachycardia.

abruptly converted to sinus rhythm (Fig. 6). The slowing ranged from prolongation of the cycle length by 40 to 220 ms (mean 79.7 ± 3.8). In 8 patients the cycle length was prolonged by more than 100 ms while 60 showed cycle length prolongation of 100 ms or less. Transient slowing was also seen when vagal maneuvers failed to terminate the tachycardia (Fig. 2 and 6). Slowing of tachycardia coincided with (1) the hypotensive phase during carotid sinus massage (Fig. 2), (2) the onset of hypertension after release of the Valsalva strain (Fig. 3) and (3) the onset of hypertension after phenylephrine (Fig. 4). In all but one patient, the tachycardias consistently stopped without passing through a phase of anterograde or retrograde block. In one exception, a patient whose tachycardia was confined to the A-V node, occasional episodes of tachycardia terminated by vagal maneuvers passed through a phase of A-V block before conversion (Fig. 7, bottom), although most episodes did not (Fig. 7, top).

Termination of paroxysmal supraventricular tachycardia with aberrant conduction: Two of the 68 patients had permanent left bundle branch block and in both the QRS configuration was identical during sinus rhythm and during paroxysmal supraventricular tachycardia. In eight patients, rate-related right (three patients) or left (five patients) bundle branch block was present during paroxysmal supraventricular tachycardia. In each of these, termination of the tachycardia by an increase in vagal tone slowed the tachycardia sufficiently to eliminate the rate-related bundle branch block for one or more cycles before termination (Fig. 8), provided the maneuver was not applied too abruptly.

Pause after termination of paroxysmal supraventricular tachycardia: The pause after termination of tachycardia ranged from 900 to 3,300 ms (mean 1683 ± 66.6). In 55 patients the pause was 2,000 ms or less and in 13 it exceeded 2,000 ms. In three patients the pause was greater than 3,000 ms, the longest pause being 3,300 ms. There were no secondary pauses that exceeded the initial pause.

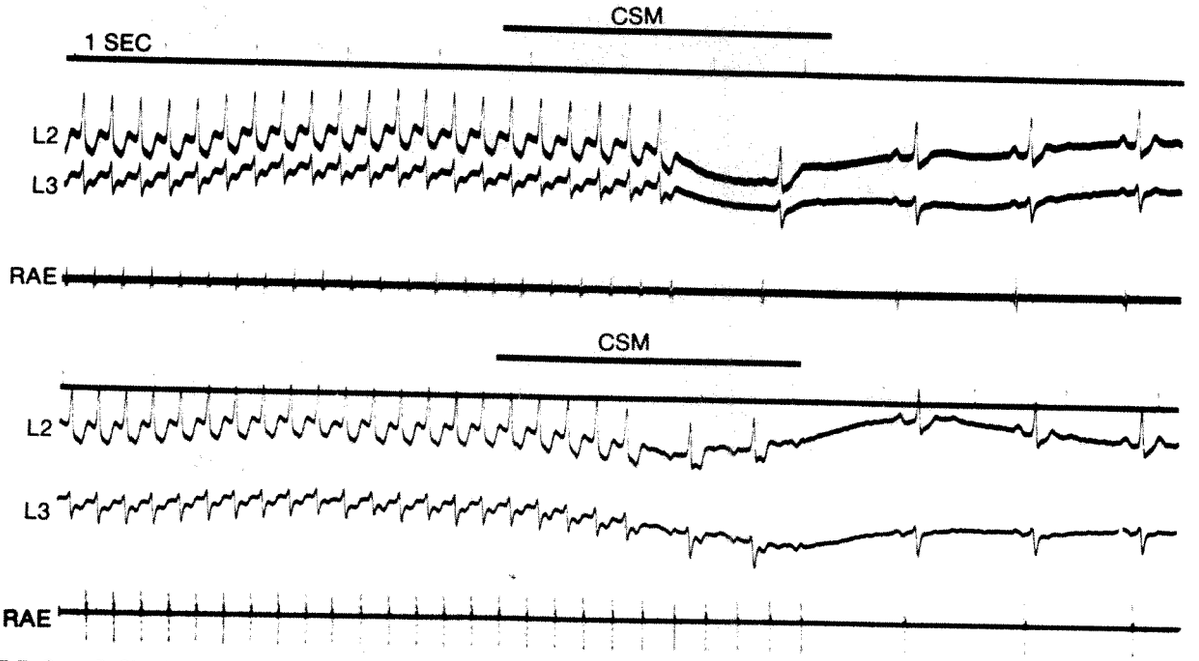


FIGURE 7. Case 5. Simultaneous recording of leads II (L2) and III (L3) and a right atrial electrogram (RAE). The first episode of tachycardia (**top**) is terminated by carotid sinus massage (CSM) (pressure) without passing through a phase of antecedent atrioventricular block. The second episode of tachycardia (**bottom**) is terminated by carotid sinus pressure but passes through a phase of atrioventricular block before terminating. Note the retrograde P waves in the surface leads.

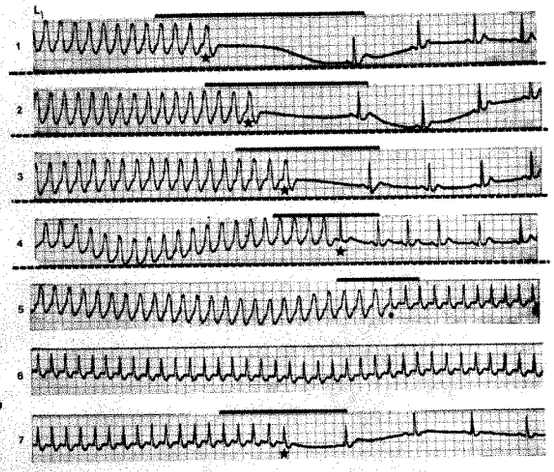


FIGURE 8. Case 6. Recording of lead I (L1) at 25 mm/s. Strips 1 to 5 record five consecutive episodes of paroxysmal supraventricular tachycardia with rate-related left bundle branch block. Several minutes separate each episode. Strips 5, 6 and 7 are continuous. Strips 1 to 5 show the effects of progressively lighter applications of carotid sinus pressure. The **stars** denote the last beat of tachycardia. In strips 1 to 3 the intensity of carotid sinus pressure was so great that the tachycardia terminated before sufficient slowing had occurred and the last beat of tachycardia shows left bundle branch block. In strip 4 a lighter application of carotid sinus pressure slowed the tachycardia sufficiently before its interruption to eliminate the bundle branch block in the last complex. In strip 5, an even lighter application of carotid sinus pressure slowed but did not terminate the tachycardia and eliminated left bundle branch block beginning with the beat with the **dot**. In strip 7 a final application of carotid sinus pressure terminated the tachycardia.

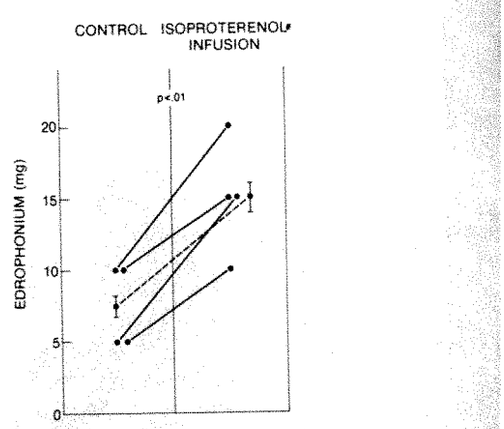


FIGURE 9. Effect of isoproterenol infusion on the minimal dose of edrophonium needed to terminate paroxysmal supraventricular tachycardia in four cases during control condition and during an infusion of isoproterenol 2 μg/min. In each case the dose of edrophonium needed to terminate the tachycardia during infusion of isoproterenol was higher than during the control period.

Effect of background sympathetic tone on vagal termination of paroxysmal supraventricular tachycardia: In four patients whose tachycardia originally terminated with carotid sinus pressure, the mean minimal dose of edrophonium needed to stop subsequent tachycardia increased from 7.5 ± 0.7 mg in control conditions to 15 ± 1.0 mg during isoproterenol infusion (Fig. 9). In parallel with the increased dose of edrophonium required, it became difficult and in some cases impossible for carotid sinus pressure by itself to terminate the tachycardia. In four patients whose tachycardia was terminated only by phenylephrine the minimal dose of phenylephrine and corresponding blood pressure elevation required was reduced by propranolol. The mean minimal phenylephrine dose decreased from a control value of 0.40 ± 0.04 to 0.25 ± 0.03 mg, and the corresponding rise in systolic blood pressure decreased from a control value of 45 ± 0.03 to 30 ± 5 mm Hg (Fig. 10).

Failure of termination of paroxysmal supraventricular tachycardia after vagal blockade: Atropine, 1.2 mg intravenously, was administered to eight patients selected randomly from group B. A subsequent paroxysm of tachycardia could no longer be terminated or transiently slowed in any of the patients by the vagal maneuvers utilized in this study.

Discussion

This study examined a fixed protocol consisting of carotid sinus pressure, Valsalva maneuver and administration of phenylephrine for terminating paroxysmal supraventricular tachycardia in 68 patients. The protocol was chosen because it was well suited to adult patients and allowed semiquantitative grading of potency. All 68 consecutive cases of paroxysmal supraventricular tachycardia could be terminated by at least one of the methods used, a finding in accordance with data from other reports[2,3,5,40–42] citing success rates of 50 to 100 percent using similar vagal maneuvers. Because we did not randomly assign matched patients to each intervention category, we cannot compare the success rate of the individual maneuvers relative to each other.

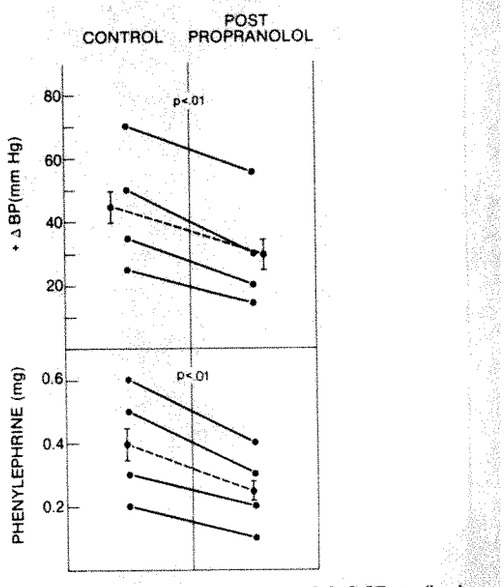


FIGURE 10. Effect of pretreatment with propranolol, 0.07 mg/kg intravenously, on the minimal dose of phenylephrine and increment in blood pressure (ΔBP) needed to terminate supraventricular tachycardia in four cases. The amount of phenylephrine and the increase in blood pressure required to terminate each case was greatly reduced by propranolol.

Relative vagal potency of various maneuvers: Potency testing suggested that administration of phenylephrine was the most potent vagal maneuver. When phenylephrine was used as a standard it was found that patients who originally belonged in this category required a larger dose of this pressor agent and higher blood pressure elevation to terminate their tachycardia than patients whose tachycardia could be terminated by carotid sinus pressure or the Valsalva maneuver. Similarly, it was found that the Valsalva maneuver was more potent than carotid sinus pressure. Other workers have also found that vasopressor therapy is the most potent vagal maneuver in terminating paroxysmal supraventricular tachycardia, with a success rate approaching 100 percent in some reports.[3,5,8,42–44]

These potency results may reflect several factors: (1) The duration of baroreceptor stimulation by the different maneuvers is variable. Carotid sinus pressure provided the shortest period of stimulation (1 to 5 seconds), whereas the pressor action of phenylephrine, which stimulated baroreceptors, was long-lasting. The duration of the Valsalva hypertensive phase was intermediate. (2) The baroreceptors stimulated are different. Carotid sinus pressure provided unilateral carotid baroreceptor stimulation, which reduces sympathetic tone, thus leading to a decrease in blood pressure.[37–39,45,46] This decrease in blood pressure is sensed by the aortic baroreceptors and the contralateral carotid sinus, tending to cause vagal tone withdrawal.[47] Depending on the relative time constants and extent of these effects, variable net increments in vagal tone will be produced by carotid sinus pressure or massage. The Valsalva maneuver and administration of phenylephrine increase blood pressure and thus stimulate all baroreceptor sites. (3) The method of application leads to variable intensity of stimulation. Carotid sinus pressure or massage is dependent on accurate location of the carotid sinus and the duration and force of compression. The Valsalva maneuver is limited by the extent of strain the patient can perform. However, phenylephrine can be given in incremental doses until a pressor response sufficient to terminate the tachycardia has been administered.

Slowing of tachycardia before termination: Slowing of paroxysmal supraventricular tachycardia before its termination has previously been described[2,3,25,33] and was seen in each case in our study. The observation is consistent with studies on vagal nerve stimulation, which prolongs the P-R interval at low intensities of stimulation and causes A-V block at high levels of stimulation.[48,49] The slowing has at least four broad clinical applications: (1) The extent of slowing of tachycardia can be used to study vagal maneuvers in a dose-dependent fashion similar to other antiarrhythmic interventions. (2) Vagal maneuvers producing transient slowing without termination may lead to a mistaken diagnosis of sinus tachycardia (Fig. 6). (3) The absence of any slowing suggests that the A-V node is not part of a tachycardia circuit or that muscarinic blockade is present.[50] (4) Sufficient slowing of tachycardia allows cases with associated rate-related bundle branch block to normalize for one or more cycles before termination. This is of diagnostic importance because some episodes of ventricular tachycardia may terminate after potent vagal maneuvers.[16,17,51] In the case of ventricular tachycardia the abnormal QRS configuration remains until sinus rhythm is restored. Depending on the rate of tachycardia, the extent of slowing and the refractory period of the bundle branches, an episode of paroxysmal supraventricular tachycardia with rate-related aberration can terminate without a phase of normalization (Fig. 8). To maximize the chances of normalization a given vagal maneuver should be applied gently.

Role of sympathetic tone: Enhanced background sympathetic tone may increase the level of vagal tone needed to terminate paroxysmal supraventricular tachycardia. Sympathetic neural tone and sympathetic agonists shorten the refractory properties of A-V nodal cells, speed conduction across this region, and attenuate the effects of the vagus nerve on this region.[49,51–55] An increase in sympathetic tone simulated by an infusion of isoproterenol increased the dose of edrophonium, a relatively pure vagal stimulant, needed to terminate paroxysmal supraventricular tachycardia. Similarly, withdrawal of the effects of sympathetic tone by pretreatment with propranolol greatly facilitated termination of tachycardia by phenylephrine. Thus, there is an active interplay between the background sympathetic tone and the increase in vagal tone required to terminate paroxysmal supraventricular tachycardia. The cases of tachycardia terminated by phenylephrine required the most potent vagal stimulation, possibly because of a high level of background sympathetic tone. The hypotensive effects[56] and the anxiety[57] produced by paroxysms of tachycardia probably elevate sympathetic tone thereby increasing the rate of tachycardia and rendering vagal termination difficult. Apart from drugs that specifically reduce sympathetic tone or enhance vagal tone, reassurance, sedation and the recumbent position may exert similar effects and hence facilitate termination of tachycardia.[18]

Complications of vagal maneuvers: In terminating paroxysmal supraventricular tachycardia in these 68 patients no complications were encountered. Asystole and ventricular fibrillation would be the most serious complications expected and have previously been reported to occur as a side effect of vigorous carotid sinus pressure or massage or edrophonium administration.[58–62] The safety of vagal maneuvers in comparison with other means of tachycardia termination remains to be defined. The longest pause was 3.3 seconds and in most cases (54 of 68) the pauses were 2 seconds or less. These short pauses following termination of paroxysmal supraventricular tachycardia may reflect the relatively young age (average 42 years) of these patients, the lack of sinus nodal and A-V nodal disease, and the graded application of more potent techniques used to increase vagal tone. The brevity of the pauses probably accounts for the absence of any serious side effects in our patient series.

Causes of failure of vagal maneuvers: We have shown that vagal maneuvers are highly effective, reproducible and safe in the termination of paroxysmal supraventricular tachycardia. When vagal techniques fail to terminate paroxysmal supraventricular tachycardia several factors may be operative: (1) There may be improper application of carotid sinus pressure by the physician or an insufficient effort at performing a Valsalva maneuver by the patient. (2) The extent of vagal and sympathetic innervation of the A-V node,[48] its responsiveness to these neural influences[49] and the background level of sympathetic tone may increase the level of vagal tone required.[54,55] (3) There may be an insufficient increase in vagal tone produced by a given amount of baroreceptor stimulation either directly by carotid sinus pressure or by maneuvers or drugs that elevate blood pressure.[63] (4) The extent of vascular reactivity in response to maneuvers that increase blood pressure may be variable.

Therapeutic implications: The type and order of vagal maneuvers that constitute the initial protocol of this study should not be construed to represent a recommended therapeutic approach in the clinical setting. Because various combinations and permutations of these and other maneuvers were not compared with each other, we are not in a position to offer such a recommendation. It may be expected that the type and order of vagal maneuvers chosen will reflect the patient's age, ability to cooperate, hemodynamic status, background cardiac condition and the clinician's preference and experience. For instance, infants and children may be upset by carotid sinus pressure and may be unable to cooperate to perform a Valsalva maneuver, whereas phenylephrine would be free of side effects. By contrast, phenylephrine or other pressor agents should not be used or used only with caution in hypertensive patients. Other vagal maneuvers such as gagging and facial immersion may also be tried prior to the use of intravenous agents.[11,12,64–66] Physiologic procedures such as the Valsalva maneuver should probably precede administration of pharmacologic agents. Drugs that reduce sympathetic tone, such as propranolol, or enhance vagal tone, such as digitalis,[67] may be administered if necessary.

In 36 of the 68 patients, the tachycardia terminated without resort to drug manipulation (with carotid sinus pressure in 33 and with the Valsalva maneuver in 3), and this effect was highly reproducible. Proper selection of patients for instruction in the use of carotid sinus pressure or the Valsalva maneuver might enable them to perform self-termination of episodes of tachycardia without requiring antiarrhythmic drugs or hospitalization. One must concede that the high success rate demonstrated may not easily be replicated by patients under conditions of stress. However, it is likely that oral therapy with antisympathetic drugs like propranolol, or enhancement of vagal tone by digitalis,[67] will increase the ease of termination and success.

Acknowledgment

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Effect of Drugs in the Wolff-Parkinson-White Syndrome

Importance of Initial Length of Effective Refractory Period of the Accessory Pathway

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The effect of procainamide, quinidine, ajmaline and amiodarone on the effective refractory period of the accessory pathway in the (A-V) anterograde and retrograde directions was studied in relation to the length of this period before drug administration. All patients had the Wolff-Parkinson-White syndrome and were studied with intracavitary recordings and programmed electrical stimulation of the heart using identical basic cycle lengths and test stimulus intervals before and after drug administration. The patients were separated into two groups, those in whom the effective refractory period of the accessory pathway was 270 ms or greater (Group 1) and those in whom it was less than 270 ms (Group 2). In the anterograde direction the magnitude of increase in the length of the effective refractory period of the accessory pathway after drug administration was related to its initial length. Only modest lengthening of this period could be accomplished in patients with an initially short period. In evaluating the effect of drugs in patients with the Wolff-Parkinson-White syndrome, the role of the initial length of the effective refractory period of the accessory pathway should be considered.

Several investigators [1-9] have reported on the effect of various drugs on the duration of the refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome. However, the significance of the initial value of the duration of the refractory period of the accessory pathway on the effect of subsequent drug administration, has not been studied. In this report we describe the effect of procainamide, quinidine, ajmaline and amiodarone on the duration of the refractory period of the accessory pathway in the anterograde and retrograde directions in relation to the initial duration before drug administration.

Methods

Patients: Fifty-nine patients were studied. Their ages ranged from 7 to 54 years; 40 were male and 19 female. In 19 patients the accessory pathway was located between the right atrium and right ventricle and in 40 patients between the left atrium and left ventricle. Patients whose accessory pathway was located in the interventricular septum were excluded because in this condition retrograde conduction over the accessory pathway is difficult to differentiate from that through the atrioventricular (A-V) node. The location of the accessory pathway was determined by the sequence of retrograde atrial activation during A-V reentrant tachycardia and during ventricular pacing [10,11].

Programmed stimulation study: After all medication was stopped for at least 5 days and informed consent had been obtained, a programmed electrical stimulation study was performed. The methods used have been described previously [10]. With use of the single test stimulus technique during atrial and ventricular pacing the effective refractory period of the accessory pathway was determined in anterograde and retrograde directions. At least three basic cycle lengths were used. The first pacing frequency was just above the sinus rate, the second was 100/min and the third 130/min. The shortest refractory period of

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the accessory pathway at the three basic cycle lengths was chosen; the maximal difference between values at the three cycle lengths was 20 ms.

The effective refractory period of the accessory pathway in anterograde direction was defined as the longest atrial premature stimulus interval that did not conduct to the ventricle over the accessory pathway from the atrial stimulation site closest to the atrial end of the accessory pathway. The effective refractory period of the accessory pathway in retrograde direction was defined as the longest right ventricular premature stimulus interval that was not followed by eccentric atrial activation (eccentric defined as atrial activation starting not in the His bundle recording or proximal coronary sinus lead, but elsewhere in the right or left atrium).

Drug protocol: Only those patients were accepted who manifested anterograde conduction over the accessory pathway during atrial pacing and retrograde conduction over the accessory pathway during ventricular pacing. After these data were obtained, drugs were given as follows: procainamide, 10 mg/kg body weight intravenously over 5 minutes (16 patients); quinidine gluconate 4 mg/kg intravenously over 5 minutes (10 patients); ajmaline, 50 mg intravenously over 3 minutes (18 patients); and amiodarone, orally, 600 mg daily during week 1 and 300 mg daily during week 2. The latter patients were restudied 2 weeks after the pre-drug investigation. Care was taken to have the intracavitary electrodes at approximately the same positions before and after drug administration. Measurements of the refractory period of the accessory pathway first in a retrograde and then in an anterograde direction were repeatedly made at identical basic cycle lengths and premature stimulus intervals as before drug administration 1 hour after procainamide and quinidine administration, 45 minutes after ajmaline was given and twice with a 15 minute interval after amiodarone. Stimulation was performed at twice threshold. Because drug administration frequently resulted in threshold changes, stimulus strength was repeatedly adjusted during the study.

The maximal changes in duration of the refractory period of the accessory pathway following drug administration were calculated by taking the shortest value of the three basic pacing lengths from pre-drug testing and comparing this value with the maximal value after drug administration at the same basic pacing cycle length. Statistical analysis was performed by using Student's paired t test.

Results

Patient groups: During the evaluation of the effect of drugs on the anterograde and retrograde refractory periods of the accessory pathway it became clear that patients could be separated into two groups:

Group 1: patients with an effective refractory period of the accessory pathway of 270 ms or longer. During evaluation of the anterograde refractory period 25 patients were in this category. The effective refractory period of the accessory pathway ranged from 270 to 520 ms with a mean value (± standard error of the mean) of 329.2 ± 37.9 ms. During evaluation of the retrograde refractory period 20 patients were in this group (range 270 to 400 ms, mean 306.5 ± 27.2 mg).

Group 2: patients with an effective refractory period of the accessory pathway of less than 270 ms. Both in the anterograde and the retrograde direction, exact determination of the refractory period was frequently impossible because the atrium or ventricle became refractory before a block in the accessory pathway developed. In the 34 patients with an anterograde refractory period of the accessory pathway of less than 270 ms, the values ranged from less than 170 to 260 ms; 18 patients had a value of 220 ms or less. There were 39 pa-

TABLE I

Relation Between Drug Response and Initial Length of Anterograde Effective Refractory Period of Accessory Pathway (ERP_{AP})

	Procainamide	Quinidine Gluconate	Ajmaline	Amiodarone
		Group 1: $ERP_{AP} \geq 270$ ms		
Patients (n)	7	5	9	4
Site of AP				
Right	3	3	3	1
Left	4	2	6	3
No change in ERP_{AP}	—	—	—	—
CB in AP	6	4	8	3
ΔERP_{AP} (ms)*	200–>300	20–>300	200–>300	50–>300
Mean*	>268.5	>222.0	>262.2	>187.5
SD*	41.8	119.1	80.4	91.8
p	<0.001	<0.05	<0.001	<0.05
		Group 2: ERP_{AP} <270 ms		
Patients (n)	9	5	9	11
Site of AP				
Right	3	1	3	2
Left	6	4	6	9
No change in ERP_{AP}	4	3	4	—
CB in AP	—	—	—	—
ΔERP_{AP} (ms)*	0–160	0–50	0–270	20–200
Mean*	31.1	18.0	51.1	77.7
SD*	51.5	21.9	86.2	43.0
p	NS	NS	NS	<0.001

* These values have to be interpreted with the knowledge that exact determination of the refractory period of the accessory pathway was frequently mpossible because the atrium became refractory before the occurrence of block in the accessory pathway.
AP = accessory pathway; CB = complete block; Δ = increase; NS = not significant; p = probability; SD = standard deviation.

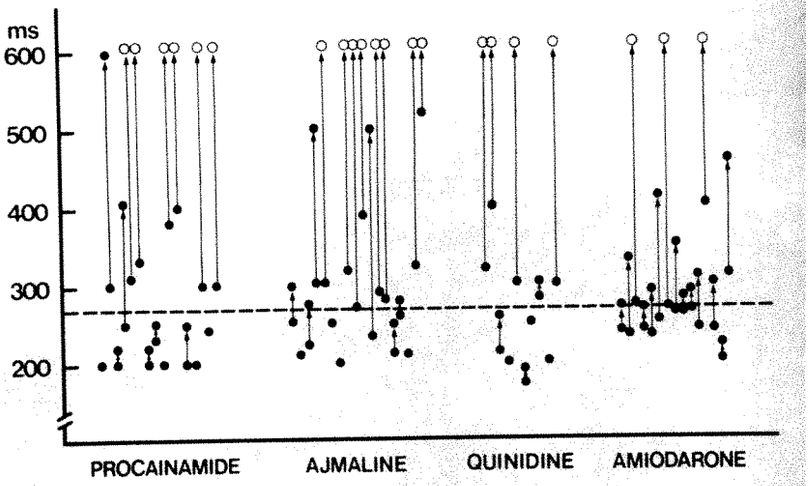


FIGURE 1. Effect of the four study drugs on the effective refractory period of the accessory pathway in the anterograde direction. The increase in duration of the effective refractory period is indicated by a **vertical arrow.** **Open circles** indicate complete block in the accessory pathway. The **broken horizontal line** indicates a refractory period of 270 ms.

tients with a retrograde refractory period of the accessory pathway of less than 270 ms (range less than 200 to 260 ms).

Effect on the effective refractory period of the accessory pathway in the anterograde direction (Table I, Fig. 1): *Group 1: patients with an effective refractory period of the accessory pathway of 270 ms or more:* All four drugs resulted in marked lengthening of the effective refractory period of the accessory pathway. Complete block in the pathway developed in six of seven patients receiving procainamide, in four of five patients after quinidine, in eight of nine patients after ajmaline and in three of four patients receiving amiodarone. Therefore, complete anterograde block in the accessory pathway was produced in 21 (84 percent) of 25 patients. No important difference was observed in the maximal amount of lengthening of the effective refractory period of the accessory pathway produced by the four drugs. Because complete block in the accessory pathway developed in several patients, exact values for the increase in duration of the refractory period cannot be given.

Group 2: patients with an effective refractory period of the accessory pathway of less than 270 ms: On the average only modest prolongation of the effective refractory period of the accessory pathway occurred in this group of patients. In 11 of the 34 patients (4 receiving procainamide, 3 receiving quinidine, 4 receiving ajmaline and none receiving amiodarone) no increase in length of the effective refractory period of the ac-

TABLE II

Relation Between Drug Response and Initial Length of Retrograde Effective Refractory Period of Accessory Pathway (ERP_{AP})

	Procainamide	Quinidine Gluconate	Ajmaline	Amiodarone
		Group 1: ERP_{AP} ≥270 ms		
Patients (n)	6	1	8	5
Site of AP				
Right	2	0	2	2
Left	4	1	6	3
No change in ERP_{AP}	—	—	1	2
CB in AP	1	—	2	—
ΔERP_{AP} (ms)*	20–>300	60	0–>300	0–90
Mean*	>123.3		>155	26
SD*	138.6		115.0	52.0
p	NS		<0.01	NS
		Group 2: ERP_{AP} <270 ms		
Patients (n)	10	9	10	10
Site of AP				
Right	4	4	4	1
Left	6	5	6	9
No change in ERP_{AP}	5	4	7	3
CB in AP	—	1	—	2
ΔERP_{AP} (ms)*	0–200	0–>340	0–280	0–>300
Mean*	40.0	>73.3	43.0	>80.0
SD*	72.8	118.9	85.4	137.1
p	<0.05	NS	NS	<0.05

* Same considerations as in Table I.
Abbreviations as in Table I.

cessory pathway was observed. Amiodarone was the only drug producing a significant increase in the duration of the effective refractory period of the accessory pathway.

Effect on the effective refractory period of the accessory pathway in retrograde direction (Table II, Fig. 2): *Group 1: patients with an effective refractory period of the accessory pathway of 270 ms or more:* No effect on the effective refractory period of the accessory pathway in the retrograde direction was seen in four patients (two receiving ajmaline and two receiving amiodarone). Complete block in the accessory pathway was seen in three patients (one receiving procainamide and two receiving ajamline). The mean increase in the effective refractory period of the accessory pathway (Table II) was less than that in the anterograde direction (Table I). Only patients receiving ajmaline showed statistically significant lengthening.

Group 2: patients with an effective refractory period of the accessory pathway of less than 270 ms: No effect on the effective refractory period of the accessory pathway was seen in 19 patients (5 receiving procainamide, 4 receiving quinidine, 7 receiving ajmaline and 3 receiving amiodarone). The other patients showed marked individual variations. In three patients (one receiving quinidine and two receiving amiodarone) complete retrograde block in the accessory pathway occurred.

Discussion

Effect of drugs on anterograde conduction of accessory pathway: Our observations indicate that the initial value of the effective refractory period of the accessory pathway played an important role in determining the effect of subsequent drug administration on the duration of this period. In the anterograde direction, when the effective refractory period of the accessory pathway was relatively long (270 ms or greater), all four drugs tested usually resulted in marked prolongation of this period, frequently to the extent of creating complete anterograde block in the accessory pathway. In patients with an initially short duration of the effective refractory period of the accessory pathway the effect was very different. Individually marked differences in the effect of various drugs on the anterograde refractory period of the accessory pathway were seen. Only amiodarone consistently resulted in moderate prolongation of this period. No role was played by a right- or left-sided location of the accessory pathway (Table I). Although, as Pritchett et al.[12] have observed, it is difficult to determine the absolute values of the effective refractory period of the accessory pathway or the exact alterations that occur after drug administration (especially when the initial period is short), the marked difference in the drug response of the two patient groups is too clear to be denied.

A practical implication of our observations is that patients with a short effective refractory period of the accessory pathway, who are at risk of high ventricular rates if atrial fibrillation supervenes and are most in need of lengthening of this period, are least likely to benefit from commercially available drugs. Our findings also raise questions concerning the morphologic or electrophysiologic differences (or both), responsible for the differences in drug responses in the two patient groups. Both procainamide and quinidine gluconate were administered more rapidly than is usual in the United States. We chose this dosage schedule because of our previous experience with its safety[3,13] and because it would give us information about the maximal effect of the drugs, which was clinically relevant to our patients who had frequent tachyarrhythmias. We[3] have previously shown that when these drug protocols are used there is a poor correlation between the electrophysiologic effects of the drug and plasma concentrations. Plasma levels become important only if continuous infusions are used or the drugs are given orally. Therefore plasma levels of the drugs were not determined during the study.

Effect of drugs on retrograde conduction of accessory pathway: In the retrograde direction the accessory pathway behaved differently. On the whole, lengthening of the effective refractory period of the accessory pathway was less marked. Complete retro-

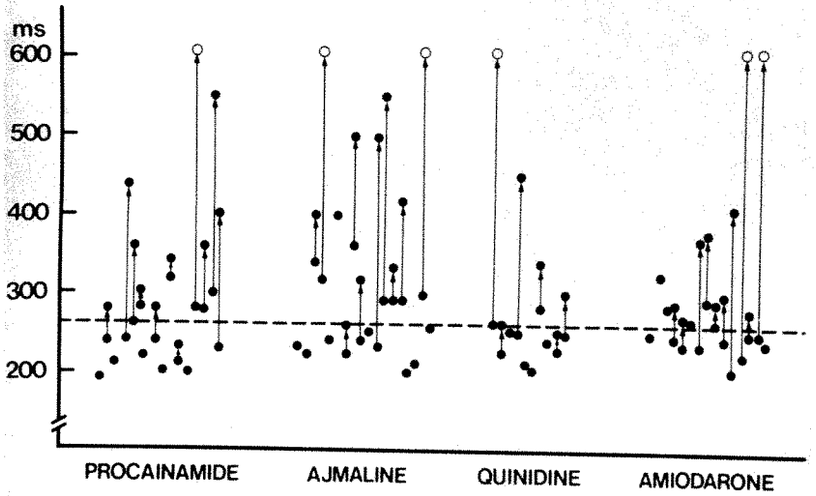


FIGURE 2. Effect of the four study drugs on the effective refractory period of the accessory pathway in the retrograde direction. Symbols as in Figure 1.

grade block after drug administration was observed in only six patients (three with an effective refractory period of the accessory pathway of less than 270 ms and three with a longer effective refractory period).

In contrast to findings in the anterograde direction, in the retrograde direction there were no important differences between drug responses in the two patient groups. However, the effect of drugs on retrograde conduction may have been influenced by the site of stimulation, which was in the apex of the right ventricle, far from the ventricular end of the accessory pathway.

As in previous studies, [3,7] our observations showed that the effect of drugs on the effective refractory period of the accessory pathway in the anterograde and retrograde directions can differ markedly. Although complete anterograde block over the accessory pathway was obtained in 21 (36 percent) of 59 patients after drug administration, complete retrograde block was observed in only 6 instances (10 percent). These findings explain why in some patients an increasing incidence of circus movement tachycardia can be seen after the administration of a drug that completely blocks anterograde conduction through the accessory pathway but has little or no effect on retrograde conduction over the accessory pathway. It is clear that observations on the effect of a drug on an intracardiac pathway in one direction can never predict the effect of that drug on the electrophysiologic properties of that pathway in the other direction.

Our data on differences in the effect of drugs on the accessory pathway in relation to the initial electrophysiologic properties of that pathway may also apply to other structures participating in the genesis of reentrant arrhythmias in the human heart. This might be an important factor responsible for differences in the effectiveness of antiarrhythmic drugs among patients.

Amiodarone and atrial fibrillation in Wolff-Parkinson-White syndrome: Among the many factors that determine the ventricular rate during atrial fibrillation in patients with the Wolff-Parkinson-White syndrome the duration of the anterograde refractory period of the accessory pathway is an important one.[14] Our data indicate that when the duration is short and there is a documented episode of atrial fibrillation with rapid ventricular rate, the protection offered by drugs known to prolong refractoriness in the accessory pathway must be individually assessed. Because factors other than the refractoriness of this pathway play a role in determining ventricular rate during atrial fibrillation, it is preferable that drugs be evaluated by the induction of atrial fibrillation before and after drug administration. However, in our study, this procedure would have required repeated cardioversions in several of our patients. In patients with a short anterograde refractory period of the accessory pathway a statistically significant lengthening of this period was observed only after administration of amiodarone. Although this increase was relatively modest, a lengthening of 75 ms in a patient with an anterograde effective refractory period of the accessory pathway of 200 ms will result in a decrease in theoretical maximal ventricular rate during atrial fibrillation from 300 to 220 beats/min. This effect of amiodarone might protect the patient with the Wolff-Parkinson-White syndrome and a short refractory period of the accessory pathway against life-threatening ventricular rates if atrial fibrillation supervenes.

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Pharmacokinetic-Hemodynamic Studies of Nitroglycerin Ointment in Congestive Heart Failure

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The aim of this study was to determine the bioavailability of nitroglycerin after application of nitroglycerin ointment in patients with heart failure and to examine whether a correlation exists between plasma nitroglycerin and its hemodynamic effects. The dose of nitroglycerin ointment selected was based on the prior hemodynamic response of individual patients to an intravenous infusion of nitroglycerin. Nine patients received 1 to 2 inches of nitroglycerin ointment on a single skin site (small dose group) and five patients received 4 inches (2 inches to two separate skin sites, large dose group).

There was good correlation between the dose of nitroglycerin ointment and bioavailability (area under the plasma concentration time curve from 0 to 240 minutes) ($r = 0.81$, $p < 0.001$). We observed a decrease in both pulmonary capillary wedge pressure and right atrial pressure 30 minutes after application of nitroglycerin ointment. The maximal changes in pulmonary capillary wedge pressure were from 28 ± 7 to 23 ± 8 mm Hg and in right atrial pressure from 14 ± 7 to 11 ± 6 mm Hg. There was a greater decrease in pulmonary capillary wedge pressure in the small dose group (31 percent) compared with the large dose group (13 percent) ($p < 0.001$). Plasma nitroglycerin concentration in the small dose group increased to 3.1 ± 3.0 ng/ml at 60 minutes and remained at that level through 240 minutes. In the large dose group a plasma nitroglycerin level of 8.9 ± 4.0 ng/ml was achieved at 60 minutes and sustained through 240 minutes. Despite this plasma nitroglycerin level there was little decline in pulmonary capillary wedge pressure. This study demonstrates a good relation between the dose of nitroglycerin ointment and nitroglycerin bioavailability; nitroglycerin ointment also provides therapeutic levels of nitroglycerin associated with substantial hemodynamic benefit in selected patients with cardiac failure.

Nitroglycerin applied to the skin in ointment form enters the circulation in a manner that bypasses the gastrointestinal tract and portal circulation. Since 1944, nitroglycerin has been adminstered percutaneously in ointment form for the therapy of peripheral circulatory disorders.[1] In 1955, Davis et al.[2] reported that this agent had favorable effects in patients with angina pectoris. This finding was later confirmed by Reichek et al.[3] who demonstrated at least a 3 hour increase in exercise capacity in patients with angina pectoris. Studies[4–6] from our own institution and elsewhere in patients with angina pectoris, myocardial infarction and congestive heart failure have demonstrated that the hemodynamic effects of nitroglycerin ointment are maximal between 60 to 90 minutes after its application and persist for at least 4 to 6 hours.

Expansion of the indications for the use of nitrate therapy has generated a need for and the development of preparations with a longer duration of action than the conventional sublingual form.[7] One such preparation is oral isosorbide dinitrate, which has been demonstrated to produce hemodynamic effects for approximately 6 hours after adminstration.[8] Although this agent is effective, in some clinical situations

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the oral route of drug administration may be unsatisfactory, for example, when the oral route is precluded by nasogastric suction or paralytic ileus or the absorption of oral agents is compromised by a malabsorption syndrome. In such patients, the percutaneous route may constitute an effective alternative. Another circumstance in which the absorption of oral medications may be both variable and incomplete is congestive heart failure.[9] Whether the percutaneous route is preferable in this setting is as yet unknown.

In previous studies of patients with heart failure a subset who did not respond to nitroglycerin ointment was identified with hemodynamic monitoring.[10,11] Because plasma levels of nitroglycerin were unavailable, the possibility existed that this lack of response resulted from an inability to achieve adequate plasma concentrations of nitroglycerin. Accordingly, we undertook a pharmokinetic-hemodynamic study of nitroglycerin ointment administered percutaneously to patients with congestive heart failure.

Our objectives were (1) to determine the bioavailability of nitroglycerin after application of nitroglycerin ointment in patients with heart failure; and (2) to examine whether a correlation exists between the concentration of nitroglycerin in plasma and its hemodynamic effects, both after application of nitroglycerin ointment and after its removal.

Methods

Patients: Fourteen patients with congestive heart failure formed the study group: There were 11 men and 3 women with a mean age of 53 years (range 38 to 67). Three had cardiomyopathy, seven had chronic arteriosclerotic heart disease and four were studied within 1 month of a myocardial infarction; these patients were all in New York Heart Association functional class III or IV[12] and refractory to conventional therapy including administration of digoxin and furosemide. Four patients with diabetes were insulin-dependent. Five had received isosorbide dinitrate for at least 3 weeks before this study. All drugs except digoxin and insulin were withheld for at least 24 hours before onset of the study.

Hemodynamic studies: After informed consent was obtained, the patients were fitted with instruments for hemodynamic monitoring in a standard fashion. This included the placement of a triple lumen thermodilution Swan-Ganz catheter in the pulmonary artery and a Teflon® cannula in the radial artery. Right atrial, pulmonary arterial and pulmonary capillary wedge pressures (obtained by balloon occlusion) and systemic arterial pressure were monitored. The cardiac output was measured, at least in duplicate, with the thermodilution technique (injection of 10 ml of ice-cold 5 percent dextrose in water into the right atrium).[13]

Intravenous nitroglycerin: Nitroglycerin was prepared for intravenous use as a 0.5 percent solution in ethanol. A 9.5 percent lactose mixture (Parke-Davis Company, Brockville, Ontario, Canada) (6.3 g) was added to ethyl alcohol (99 percent) to a total volume of 120 ml. The alcoholic supernatant was decanted and passed through a 0.22 Millex® millipore filter. The solution was assayed using a spectrophotometric technique before being reassayed using our gas-liquid chromatographic method.[14] Immediately before use, the nitroglycerin solution was added to 5 percent dextrose in water and contained in glass bottles to produce a concentration of 100 μg/ml.

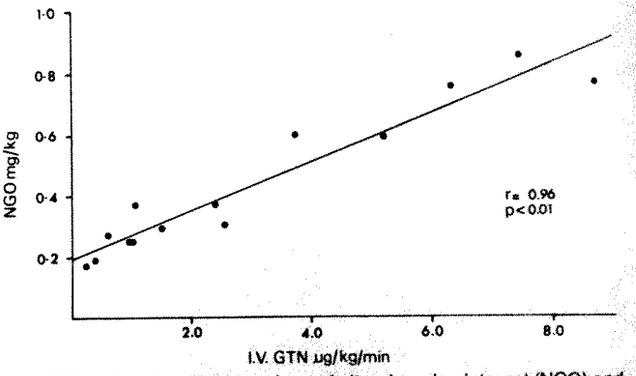


FIGURE 1. Relation between dose of nitroglycerin ointment (NGO) and peak intravenous nitroglycerin (I.V. GTN) infusion rate. p = probability; r = correlation coefficient.

After a control period of 30 minutes, during which the hemodynamic measurements were demonstrated to be reproducible, intravenous nitroglycerin was infused at an initial rate of 15 to 20 μg/min. The aim was to reduce pulmonary capillary wedge pressure by at least 25 percent, and the infusion was increased in stepwise fashion (50 percent increments of prior rate) every 10 to 15 minutes until either the desired hemodynamic end point was achieved or a greater than 10-fold increment in the initial infusion rate had been reached. The final infusion rate was maintained until a hemodynamic steady state was achieved, which required approximately 15 to 20 minutes. The infusion was then discontinued and monitoring performed for at least an additional 30 to 60 minutes until return to control hemodynamic values had been demonstrated.

Nitroglycerin ointment groups: We[15,16] have previously found that the hemodynamic response to intravenous nitroglycerin is useful in establishing the response to and selecting the dose of other forms of nitrate therapy.[15,16] In this study, patients in whom the hemodynamic end point was reached at an intravenous nitroglycerin infusion rate of 2.5 μg/kg per min or less received 2 inches (5 cm) or less of nitroglycerin ointment. The nine patients in this group had mean (± standard deviation) intravenous nitroglycerin infusion rate of 1.2 ± 0.8 μg/kg per min. Patients who received more than 2.5 μg/kg per min of intravenous nitroglycerin received 4 inches (10 cm) of nitroglycerin ointment. Among the five patients in this group, the hemodynamic end point was reached in only one, and the average intravenous nitroglycerin infusion rate was 6.3 ± 1.9 μg/kg per min. The relation between the dose of intravenous nitroglycerin and nitroglycerin ointment is shown in Figure 1. Detailed examination of the pharmacokinetic-hemodynamic response to intravenous nitroglycerin in nine of our patients has been reported separately.[16]

Nitroglycerin ointment (Nitrol® 2 percent, Kremers-Urban Company, Milwaukee, Wisconsin) was applied to the chest or flank over a 3 by 3 inch (7.6 by 7.6 cm) square area. As indicated, the dose selected was based on the patient's response to prior intravenous administration of nitroglycerin (Fig. 1). When more than 2 inches was applied, a second 3 by 3 inch site was utilized. After application of nitroglycerin ointment, hemodynamic monitoring was performed at frequent intervals through 240 minutes: In selected instances the period of monitoring was prolonged to 480 minutes. The occlusive dressing was then removed, the residual ointment scraped from the skin and the skin site washed with alcohol.

Arterial blood samples were withdrawn during the control period before the administration of intravenous nitroglycerin

TABLE I

Summary of Hemodynamic Response to Nitroglycerin Ointment (n = 14)

Time Period (mm)	HR	PCW	RAP	MAP	CI	SI	TPR
C	93 ± 16	28 ± 7	14 ± 7	93 ± 20	2.2 ± 0.7	23.9 ± 8.3	22.3 ± 10.4
30	93 ± 15	24 ± 8	12 ± 6	90 ± 17	2.3 ± 0.6	25.5 ± 6.5	20.4 ± 8.6
60	93 ± 15	24 ± 8	11 ± 6	90 ± 20	2.3 ± 0.6	24.9 ± 6.8	20.7 ± 8.2
90	92 ± 15	24 ± 8	12 ± 7	89 ± 21	2.3 ± 0.5	25.1 ± 4.0	20.6 ± 9.5
120	92 ± 15	23 ± 8	11 ± 6	90 ± 20	2.3 ± 0.5	25.0 ± 6.8	21.0 ± 8.6
240	91 ± 15	24 ± 9	12 ± 8	86 ± 18	2.4 ± 0.7	27.6 ± 9.3	19.9 ± 9.7
p	NS	<0.0005	<0.0005	NS	<0.05	<0.02	NS

All summary values represent mean ± standard deviation; p values represent a linear regression analysis performed on average percent from control value (t = 0) against time.

C = control value; CI = cardiac index (liters/min per m^2; HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); NS = not significant; PCW = pulmonary capillary wedge pressure (mm Hg); RAP = right atrial pressure (mm Hg); SI = stroke index (ml/beat per m^2); TPR = total peripheral resistance (units).

as well as just before the application of nitroglycerin ointment and at 60, 90 and 240 minutes after the application of ointment. In some instances, additional samples were available up to and including 480 minutes as well as 30 minutes after the removal of nitroglycerin ointment. Blood samples were immediately centrifuged at 5° C and the decanted plasma was frozen at −20° C. Subsequent analysis was performed using a gas-liquid chromatograph with isosorbide dinitrate or dinitrobenzene as the internal standard (14).

Analysis of data: Derived calculations were performed using the formulas SI = CI/HR and TPR = MAP-RAP/CO, where SI = stroke index in ml/beat per m^2, CI = cardiac index in liters/min per m^2, TPR = total peripheral resistance in units, MAP = mean arterial pressure in mm Hg, CO = cardiac output in liters/min and RAP = right atrial pressure in mm Hg.

Statistical comparisons of measurements were made using regression analysis and Student's t test with paired and unpaired observations used when appropriate. The correlations and their significance were tested using Fisher's F test. The area under the plasma concentration time curve (from 0 to 240 minutes and from 0 to 480 minutes) was determined with trapezoidal integration using discrete points.

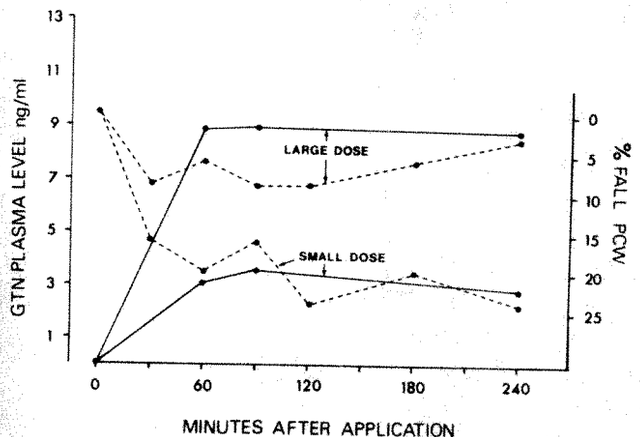


FIGURE 2. Plot of the relation between plasma nitroglycerin (glyceryl trinitrate) (GTN) concentration (**solid lines**) and percent decrease in pulmonary capillary wedge pressure (PCW) (**dashed lines**) for the groups receiving small dose (2 inches or less) and large dose (4 inches) of nitroglycerin ointment. Standard deviations for plasma nitroglycerin and percent reduction in pulmonary capillary wedge pressure are equal to or less than ±4.3 ng/ml and ±11.5 percent, respectively, in the large dose group and equal to or less than ±3.1 ng/ml and ±9.5 percent in the small dose group.

Results

The relation between the dose of nitroglycerin ointment selected and the peak nitroglycerin infusion rate (that is the dose that either produced a 25 percent reduction in pulmonary capillary wedge pressure or was greater than 10 times the initial infusion rate) is illustrated in Figure 1. A regression analysis performed between the doses of the two modes of nitroglycerin adminstration demonstrates a good correlation (r = 0.96, probability [p] <0.01).

Hemodynamic response to nitroglycerin: Table I presents a summary of the hemodynamic response to nitroglycerin ointment at time periods up to and including 240 minutes after application. To determine the effect of treatment, a linear regression analysis was performed on the percent change from the control level (t = 0 value) against time. No significant changes were observed in heart rate, mean arterial pressure or total peripheral resistance. In all cases the slope of the line was not significantly different from 0 (typically t value < 1.8), suggesting that there is no consistent change in level with time. For pulmonary capillary wedge pressure, the average percent reduction, as measured by the intercept of the fitted line, was 15 percent with a t value of 5.8 (p <0.0005); for right atrial pressure, the percent reduction was 19 percent (t = 4.8, p <0.0005); for cardiac index, the percent increase was 8 percent (t = 2.1, p <0.05); for stroke index, the percent increase was 8 percent (t = 2.4, p <0.02).

Relation between bioavailability of nitroglycerin ointment and peak hemodynamic effect (Table II): Changes in pulmonary capillary wedge pressure and right atrial pressure proved to be the most sensitive indicators of the hemodynamic response to nitroglycerin in our previous studies, and therefore the peak changes in these measurements are shown in Table II.[15,16] We

TABLE II

Relation Between Bioavailability of Nitroglycerin Ointment and Peak Hemodynamic Effect

	Dose of NGO		Nitroglycerin Bioavailability	Peak Hemodynamic Effect			
				Control PCW	Decrease in PCW	Control RAP	Decrease in PCW
Case	(inches)	(mg/kg)	AUC_{0-240} (ng·min/ml)	(mm Hg)	(%)	(mm Hg)	(%)
			Small Dose Group (n = 9)				
1	1.0	0.17	325	18	28	6	33
2	1.25	0.19	233	21	33	8	13
3	1.5	0.25	684	25	44	8	38
4	1.5	0.25	905	21	52	8	63
5	1.5	0.27	525	28	29	8	50
6	1.5	0.29	970	24	17	17	24
7	1.5	0.30	263	40	25	27	33
8	2.0	0.37	1752	30	23	12	33
9	2.0	0.37	490	24	25	22	32
Mean		0.27	683	26	31*	13	37*
SD		0.07	480	7	11	7	15
			Large Dose Group (n = 5)				
10	4.0	0.59	1467	35	9	16	25
11	4.0	0.60	1452	33	15	16	13
12	4.0	0.75	2901	26	19	14	50
13	4.0	0.76	2483	42	14	24	25
14	4.0	0.86	1424	27	7	20	5
Mean		0.71	1945	33	13†	18	24†
SD		0.11	698	7	5	4	17
			Both Groups (n = 14)				
Mean		0.43	1134	28	24*	15	24*
SD		0.23	828	7	13	7	19

Statistical significance: Paired *t* test (percent decrease in pulmonary capillary wedge and right atrial pressures): * $p < 0.001$; † $p < 0.025$. Unpaired *t* test (small dose versus large dose group) for area under the concentration-time curve, control value and percent decrease in pulmonary capillary wedge pressure and control value and percent decrease in right atrial pressure: $p < 0.005$, < 0.005, < 0.005, NS and NS, respectively.

AUC = area under concentration-time curve; NGO = nitroglycerin ointment; NS = not significant; PCW = pulmonary capillary wedge pressure; RAP = right atrial pressure; SD = standard deviation.

have arbitrarily divided the data into two subsets based on the dose of nitroglycerin ointment applied. The small dose group (n =9) received 1 to 2 inches or 12.5 to 25 mg of nitroglycerin ointment on a single skin site. The large dose group (n = 5) received 4 inches or 50 mg of nitroglycerin ointment (2 inches applied to two separate skin sites). The control value of pulmonary capillary wedge pressure was higher in the large than in the small dose group, (33 versus 26 mm Hg, $p < 0.005$). After application of nitroglycerin ointment there was a greater decrease in pulmonary capillary wedge pressure in the small (31 percent) than in the large dose group (13 percent, $p < 0.005$). There was no significant difference in the control value or in the changes in right atrial pressure between the two groups. The area under the plasma concentration-time curve from 0 to 240 minutes was significantly less in the small than in the large dose group ($p < 0.005$).

Changes in pulmonary capillary pressure correlated with plasma nitroglycerin concentration: In Figure 2, the percent changes from the control value of pulmonary capillary wedge pressure are displayed over the 240 minute period after application of nitroglycerin ointment to allow for comparison with plasma nitroglycerin concentration data in the large and small dose groups. In the small dose group, pulmonary capillary wedge pressure decreased substantially at 30 minutes, reaching its maximal reduction of 23 percent at 120 minutes and remaining depressed through 240 minutes. Plasma nitroglycerin concentration in this group increased to 3.1 ± 3.0 (standard deviation) ng/ml at 60 minutes and remained at that level throughout the remainder of the sampling period. In the large dose group a plasma nitroglycerin level of 8.9 ± 4.0 ng/ml was achieved at 60 minutes and was sustained throughout the 240 minute sampling period. Despite this plasma nitroglycerin concentration there was little decline in pulmonary capillary wedge pressure.

We analyzed the decrease in pulmonary capillary wedge pressure produced by nitroglycerin ointment as a function of resting pulmonary capillary wedge pressure, cardiac index and total peripheral resistance and found that none of these indexes were of value in predicting the change in pulmonary capillary wedge pressure after application of nitroglycerin ointment ($r \leq 0.53$, in all instances).

In four patients (Cases 4, 10, 11 and 14), hemodynamic and plasma nitroglycerin data were available for 480 minutes after application of nitroglycerin ointment (Fig. 3). There was a modest early reduction in right atrial pressure that was sustained through 360 minutes and returned toward the control value at 480 minutes. There was a small and sustained reduction in pulmonary capillary wedge pressure. The plasma nitroglycerin

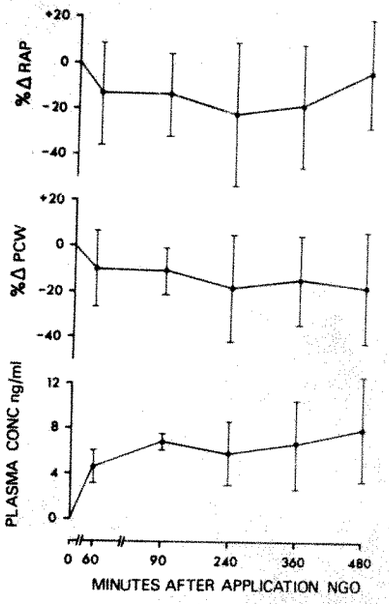


FIGURE 3. Hemodynamic and plasma nitroglycerin data in four patients studied for 480 minutes after application of nitroglycerin ointment (NGO). All data represent mean values ± standard deviations. CONC = concentration; PCW = pulmonary capillary wedge pressure; RAP = right atrial pressure.

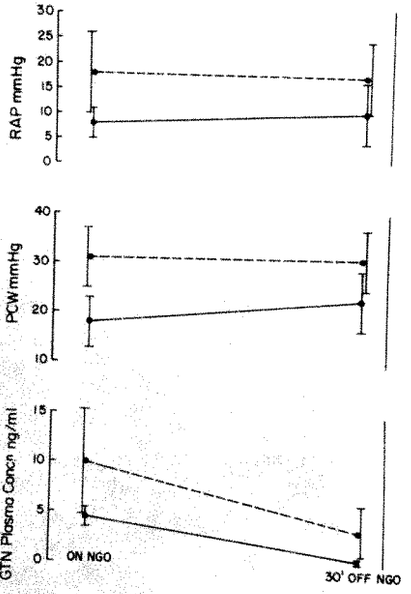


FIGURE 4. Influence of removal of nitroglycerin ointment (NGO) in 11 patients. "On NGO" indicates the last observation before removal. Seven patients are in the small dose group (**solid lines**) and four in the large dose group (**dashed lines**). Significant changes occurred in pulmonary capillary wedge pressure (PCW) in the small dose group (18 to 23 mm Hg, $p < 0.025$) and in nitroglycerin (GTN) plasma concentration ($p < 0.05$ for both groups). The plasma concentration data in the small dose group are based on values in three patients.

levels were elevated to nearly 5 ng/ml at 60 minutes and remained elevated through the balance of the sampling period.

In four patients in the large dose group and in seven in the small dose group, we analyzed the effects of removing nitroglycerin ointment. Six patients were studied to 240 minutes, two to 360 minutes and three to 480 minutes (Fig. 4). There was little change in either right atrial or pulmonary capillary wedge pressure in the large dose group 30 minutes after removal of nitroglycerin despite a substantial decrease in plasma nitroglycerin. By contrast, in the small dose group there was a slight rise in right atrial pressure and a significant increment in pulmonary capillary wedge pressure 30 minutes after removal of nitroglycerin. Plasma nitroglycerin, available in three patients in the small dose group, showed a sharp decrease similar to that noted in the large dose group.

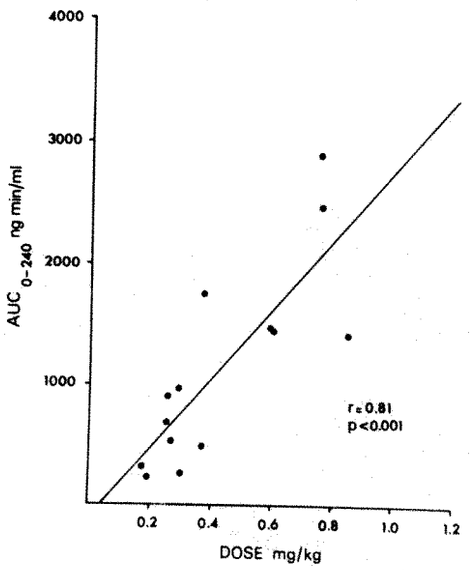


FIGURE 5. Linear regression analysis of relation between the area under the plasma concentration-time curve from 0 to 240 minutes (AUC_{0-240}) and dose of nitroglycerin ointment for the total study group ($r = 0.81$; $p < 0.001$).

The relation between plasma nitroglycerin concentration and the dose of nitroglycerin ointment applied was testing using a linear regression analysis. In all patients the relation between peak plasma nitroglycerin and dose of nitroglycerin ointment in mg/kg was $r = 0.89$ ($p < 0.001$); the relation between the area under the concentration-time curve (AUC_{0-240}) and dose of nitroglycerin ointment was $r = 0.81$ ($p < 0.001$) (Fig. 5). The best relation was observed in the four patients shown in Figure 3 in whom the correlation between the area AUC_{0-480} and the dose of nitroglycerin ointment was 0.98 ($p < 0.02$).

Discussion

Bioavailability of nitroglycerin ointment: This study documents the bioavailability of nitroglycerin when delivered percutaneously to patients with congestive heart failure. There was in general a good relation between the area under the plasma concentration-time curve from 0 to 240 minutes and the dose of nitroglycerin ointment (Fig. 5). This relation improved

when it was examined in the four patients who were observed for 480 minutes after application of nitroglycerin ointment (Fig. 3). The previously demonstrated short half-life of nitroglycerin of 1.9 minutes coupled with the observation of sustained plasma nitroglycerin levels 480 minutes after application of nitroglycerin ointment indicates that absorption of nitroglycerin must have continued throughout the entire period of application.[16] This suggests that "flip-flop" kinetics are operative when nitroglycerin ointment is applied; that is, the plasma concentration over the study period is directly dependent on continuing absorption.[17]

Despite the good relation between dose of nitroglycerin ointment and area under the plasma concentration-time curve from 0 to 240 minutes, some interpatient variability occurred. There are a variety of reasons why interpatient differences in bioavailability might be expected after application of similar doses of nitroglycerin ointment. These differences relate in part to variations in percutaneous absorption as modulated by skin perfusion, permeability and thickness. Moreover, differences in both systemic perfusion and venous congestion in these patients with heart failure would be expected to alter volume of distribution, rate of hepatic metabolism and, therefore, clearance of nitroglycerin.[18] The interpatient variability would probably have been diminished had all patients been evaluated throughout the complete time course of absorption, which is as yet unknown.

Examining our data in the light of the experimental studies of Horhota and Fung[19] is of considerable interest. These investigators studied the effects of topical application of nitroglycerin ointment to the abdominal skin surface of rats; they demonstrated a wide variation in the nitroglycerin plasma concentration-time curve among individual rats despite similar doses. They also found that the concentration of blood nitroglycerin remained elevated throughout the duration of the 4 hour study period. Analysis of surface sections after the 4 hour absorption experiments revealed that nearly 60 percent of the applied drug could be recovered, indicating that significant quantities of the drug were still available for absorption. Although in the current study we found that plasma nitroglycerin decreased substantially after removal of nitroglycerin ointment, it was still detectable 30 minutes thereafter. This finding was unexpected in view of the short half-life of nitroglycerin of 1.9 minutes and it suggests that a depot for nitroglycerin exists in the skin of human subjects, as it does in rats, after percutaneous application.[16]

Beneficial hemodynamic effects of nitroglycerin ointment: This study confirms that nitroglycerin ointment provides prompt and sustained hemodynamic benefit in selected patients with congestive heart failure. The patients in the small dose group who were characterized as sensitive to nitroglycerin by prior intravenous nitroglycerin infusion demonstrated hemodynamic benefit concomitant with the appearance of approximately 3 ng/ml of nitroglycerin in plasma. The hemodynamic effects were already clearly evident 30 minutes after application of nitroglycerin ointment at a time when the plasma level was probably less than 3 ng/ml (Fig. 2). This concentration of nitroglycerin is within the therapeutic range of 1.2 to 11.1 ng/ml defined in our previous study of 16 patients with congestive heart failure who received intravenous nitroglycerin.[16]

Although there appeared to be a good correlation between plasma nitroglycerin and its hemodynamic effects in the small dose group, a subset of patients has again been identified who demonstrate minimal response to nitroglycerin despite achieving plasma concentrations of 9 ng/ml. These findings were anticipated from the patients' prior attenuated response to intravenous nitroglycerin. The attenuated response in these patients is also demonstrated by the lack of hemodynamic alteration after removal of nitroglycerin ointment despite a substantial decrease in plasma nitroglycerin.

We[16] have previously shown that some patients with heart failure may respond to nitroglycerin with a reduction in right atrial pressure, but little change in left ventricular filling pressure.[16] This appeared to be the case in Patients 10, 12 and 13 and may be partly related to asymmetric distribution of cardiac disease expressed by differing compliance characteristics of the two ventricles.[20]

Factors influencing response to nitroglycerin: A variety of factors may have influenced the response to nitroglycerin in this study. Nitrate responsiveness could not be predicted from the value of the resting cardiac index, total peripheral resistance or pulmonary capillary wedge pressures.[21] Three of the five patients in the large dose group had diabetes, and two of these three were insulin-dependent; small vessel disease secondary to the diabetes could have modified the hemodynamic response in these patients. Prior nitrate therapy did not appear to be a predictor of response to nitroglycerin ointment because only two of the five patients who received prior nitrate therapy were in the large dose group.[22] The amount of circulating catecholamines and angiotensin is known to be increased in some patients with heart failure; variations in the levels of these substances would also be expected to alter the response of the peripheral circulation to pharmacologic therapy.[23,24] Because the concentration of nitroglycerin in plasma was in the therapeutic range in the patients who did not respond, absorption of the drug from ointment was confirmed. Lack of response was not due to failure of drug delivery but probably represented target organ resistance in peripheral arterioles and veins. This resistance cannot be predicted from control hemodynamic indexes, but it can be anticipated by prior intravenous nitroglycerin infusion and is best detected by hemodynamic monitoring.

Clinical implications: From these data we conclude that nitroglycerin ointment provides therapeutic levels of nitroglycerin that are associated with substantial hemodynamic benefit in selected patients with heart failure. Therapeutic plasma concentrations of nitroglycerin are demonstrable through at least 480 minutes and probably persist for a longer period. In those cases in which an attenuated response is found during intra-

venous infusion of nitroglycerin, large doses of nitroglycerin ointment (4 inches) are also unlikely to be of benefit. Further investigation is required to (1) document the complete time course of nitroglycerin bioavailability and hemodynamics after application of nitroglycerin ointment, (2) explore the mechanism of resistance of nitroglycerin, and (3) determine whether tolerance occurs in responsive patients.

Acknowledgment

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Simultaneous Anterograde Fast-Slow Atrioventricular Nodal Pathway Conduction After Procainamide

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Three patients with paroxysmal supraventricular tachycardia underwent electrophysiologic studies that included His bundle recordings, incremental atrial and ventricular pacing and extrastimulation before and after intravenous infusion of 500 mg of procainamide. In all three patients the tachycardia was induced during atrial pacing or premature atrial stimulation, or both. Two of the three patients had discontinuous atrioventricular (A-V) nodal curves with induction of a slow-fast tachycardia during failure in anterograde fast pathway conduction and one patient had a smooth A-V nodal curve with induction of a slow-fast tachycardia at critical A-H interval delays. After procainamide: (1) in all three patients atrial pacing induced A-V nodal Wenckebach periodicity (cycle length 300 to 400 ms) resulting in simultaneous anterograde fast and slow pathway conduction (one atrial beat resulting in two QRS complexes) and retrograde fast pathway conduction initiating an echo response or a slow-fast tachycardia, or both; (2) in all three patients there was enhanced conduction and shortening of refractoriness of the anterograde fast pathway and depressed conduction and lengthening of refractoriness of the retrograde fast pathway; and (3) in two patients there was inability to sustain tachycardia because of selective block within the retrograde fast pathway. In conclusion: (1) procainamide altered conduction and refractoriness of the anterograde fast and slow pathways so that simultaneous conduction could occur during atrial pacing, resulting in a double ventricular response and a slow-fast echo or tachycardia, or both; and (2) the differential effects of procainamide on anterograde fast and retrograde fast pathways suggests two functional A-V nodal fast pathways, one for anterograde and the other for retrograde conduction.

Electrophysiologic studies have established reentry within the atrioventricular (A-V) nodal region as the most common mechanism of paroxysmal supraventricular tachycardia.[1–8] These studies have also revealed that, although in some patients the induction of A-V nodal reentrant tachycardia is associated with failure in anterograde fast pathway conduction resulting in anterograde conduction solely in the slow pathway and retrograde conduction over the recovered anterograde fast pathway,[4–6] in others the induction of A-V nodal reentry is associated with attainment of a critical A-V nodal conduction delay and retrograde conduction over a fast retrograde pathway.[2,9] Nonetheless, reciprocation within a slow and fast pathway in the region of the A-V node is believed to be the electrophysiologic basis of A-V nodal reentry. In contrast, simultaneous anterograde fast and anterograde slow pathway conduction resulting in a slow-fast tachycardia is exceedingly rare.[10] In this paper we describe (1) the electrophysiologic findings in three patients with A-V nodal reentry who demonstrated simultaneous anterograde fast and slow pathway conduction resulting in a double ventricular response and a slow-fast echo or tachycardia, or both, after the administration of procainamide; and (2) differential effects of procainamide on the anterograde and retrograde fast pathways. The implications of these observations are discussed.

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Methods

Study patients: Three patients with a history of palpitations and electrocardiographically documented paroxysmal supraventricular tachycardia were studied after the nature of the procedure was explained and signed consent obtained. One patient had atherosclerotic heart disease and the remaining two patients had no evidence of cardiac disease. None had a recent myocardial infarction, electrolyte or metabolic abnormalities or the Wolff-Parkinson-White syndrome and none had received any cardioactive medications for at least 4 days before the study.

Electrophysiologic study: Three quadripolar catheters were introduced percutaneously under local anesthesia and positioned in the region of the high right atrium, at the level of the tricuspid valve for recording His bundle activity[11] and in the right ventricular apex. The proximal poles of the atrial and ventricular catheters were utilized for recording and the distal poles for stimulation. Two or more standard electrocardiographic leads, intracardiac electrograms at frequency settings of 40 to 500 hertz and time lines generated at 40,200 and 1,000 ms were displayed on a multichannel oscilloscope (VR-12, Electronics for Medicine, White Plains, New York) and reproduced on thermal paper at a paper speed of 100 to 150 mm/s.

Atrial and ventricular pacing were performed up to the onset of anterograde and retrograde block or up to a heart rate of 220 beats/min. During pacing-induced A-V nodal Wenckebach cycles, the stimulator was periodically turned off for observation of subsequent spontaneous events. The atrial and ventricular extrastimulus techniques were employed to determine the refractory periods of the atrioventricular (A-V) and ventriculoatrial (V-A) conduction system at two or more cycle lengths. After completion of control studies, procainamide in a total dose of 500 mg was administered intravenously at a rate of 50 mg/min and studies were repeated within 10 minutes of drug administration. Blood samples for serum procainamide levels were drawn in all three patients.

Definition of terms: ***Anterograde conduction intervals and refractory periods:*** These were defined as previously described.[12]

Retrograde conducting intervals and refractory periods: *V-A conduction time* was measured from the stimulus artifact during ventricular pacing to the onset of the retrograde low septal atrial electrogram on the His bundle tracing.

S_2-H_2 interval was measured from the onset of the premature stimulus artifact (S_2) to the onset of the retrograde His bundle electrogram (H_2)

H_2-A_2 interval was measured from the onset of the retrograde His bundle deflection (H_2) to the onset of the retrograde low septal electrogram (A_2) on the His bundle tracing.

Retrograde functional refractory period of the V-A conduction system was defined as the shortest A_1-A_2 interval in response to any range of S_1-S_2 or V_1-V_2 intervals.

Retrograde effective refractory period of the V-A conduction system was defined as the longest S_1-S_2 or (V_1-V_2) interval at which S_2 or V_2 failed to evoke an A_2 response. This interval is determined by the His-Purkinje system when S_2 is not followed by H_2, provided that H_2 is identified before block or by the A-V nodal region, in which case the retrograde His bundle deflection (H_2) is not followed by A_2.

Retrograde functional and effective refractory periods of the His-Purkinje system and the effective refractory period

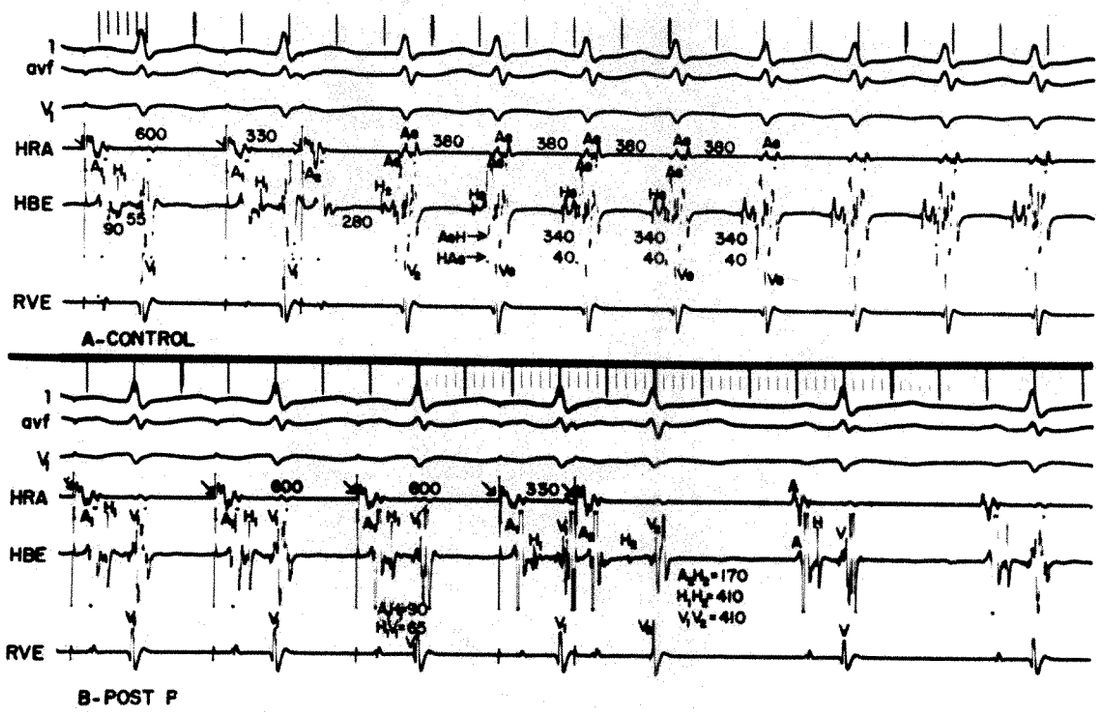


FIGURE 1. Case 1. Atrial premature stimulation during control study (**A**) and after administration of procainamide CP (**B**). **From top to bottom** in each panel: I, avf and V_1 = surface electrocardiographic leads; HRA = high right atrial electrogram; HBE = His bundle electrogram and RVE = right ventricular electrogram. **A**, at a coupling interval of 330 ms, the A_2-H_2 interval increased to 280 ms, resulting in a sudden jump in the H_1-H_2 curve (H_1-H_2 = 530 ms) with initiation of a reentrant supraventricular tachycardia. The cycle length of the tachycardia is 350 ms, the Ae-H interval is 340 ms and the H-Ae interval is 40 ms. **B**, after procainamide, at a similar coupling interval of 330 ms, the A_2-H_2 interval is 170 ms and the H_1-H_2 interval is 410 ms, both shorter than control values. Also note the inability to initiate a tachycardia.

TABLE I

Anterograde Conduction and Refractory Periods (ms) Before and After Procainamide (P)

	Case 1		Case 2		Case 3	
	Control	After P	Control	After P	Control	After P
A-H interval	90	90	75	70	75	60
H-V interval	55	65	35	40	50	55
A-H increase before WB	90 → 140	90 → 130	75 → 150	70 → 130	75 → 260	60 → 200
ACL for WB	350	330	450	400	300	300
Fast pathway						
FRP	405	390	500	470	<350	<300
ERP	340	NA(<305)	440	400	NA(<280)	NA(<270)
Slow pathway						
FRP	520	...	785	780	...	...
ERP	270	...	380	350	...	...
Atrial pacing cycle length	600	600	600	600	600	600

ACL = atrial cycle length; ERP = effective refractory period; FRP = functional refractory period; NA = not attained; WB = Wenckebach block.

of the ventricular myocardium were defined as previously described.[13,14]

The presence of anterograde and retrograde discontinuous A-V nodal curves and the refractory periods of the anterograde fast and slow pathways were determined as previously described.[4-6,9]

Results

In all three patients paroxysmal supraventricular tachycardia could be induced during atrial pacing-induced A-V nodal Wenckebach periodicity or during premature atrial stimulation, or both. The reentrant nature of the tachycardia was suggested by previously established criteria.[2,3,9,15] The utilization of V-A bypass tracts in the reentrant process was excluded on the basis of the following criteria: (1) the retrograde echo (Ae) occurred simultaneously or almost simultaneously with the ventricular electrogram[8,9,15]; (2) the H-Ae/Ae-H ratio ranged from 1:2.1 to 1:8.5[8,9]; (3) ventricular stimulation during tachycardia when the His bundle was refractory did not result in atrial preexcitation[16,17]; and (4) during ventricular premature stimulation, A_2 moved out of the ventricular electrogram more or less in parallel with H_2.[8,9]

Electrophysiologic data during control studies and after procainamide are presented in Tables I and II. Serum procainamide levels were 8 to 15 mg/liter.

Case Reports

Case 1: This was a 70 year old man with recurrent paroxysmal supraventricular tachycardia. Control conduction studies during sinus rhythm revealed an A-H interval of 90 ms and an H-V interval of 55 ms. Incremental atrial pacing resulted in progressive prolongation of the A-H interval (90 to 140 ms) before the occurrence of A-V nodal Wenckebach periodicity. Atrial pacing-induced A-V nodal Wenckebach periodicity initiated sustained supraventricular tachycardia. Atrial premature stimulation studies demonstrated a discontinuous A-V nodal curve with initiation of supraventricular tachycardia during failure in anterograde fast pathway conduction. The critical A-H interval for induction of tachycardia ranged from 280 to 370 ms (Fig. 1A). The functional and effective refractory periods of the anterograde fast pathway were 405 and 340 ms and that of the anterograde slow pathway 520 and 270 ms, respectively.

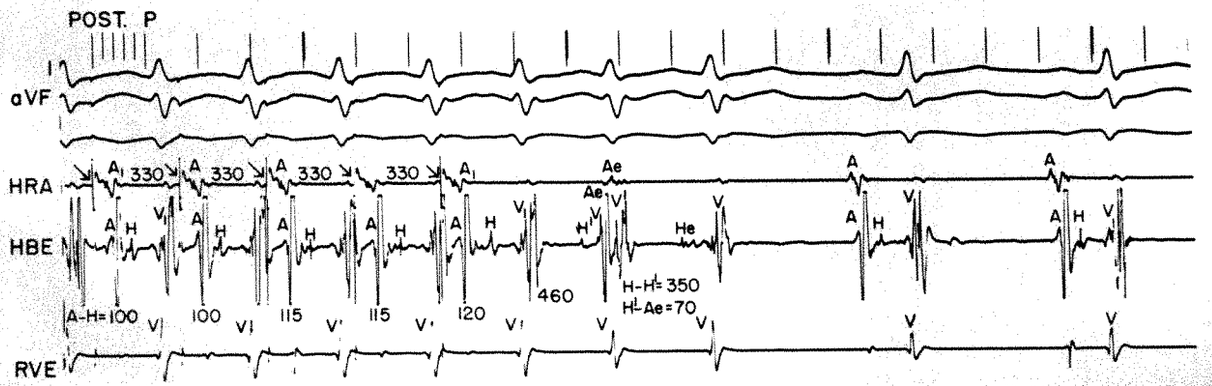


FIGURE 2. Case 1. Atrial pacing after administration of procainamide (P). Atrial pacing at a cycle length of 330 ms results in Wenckebach periodicity. After the fifth paced beat the stimulator is turned off. The last paced beat of the Wenckebach sequence results in two QRS complexes due to simultaneous conduction in both the anterograde fast (A-H = 120 ms) and anterograde slow pathway (A-H′ = 460 ms) and an echo response with an H′-Ae interval of 70 ms, which is longer than the control value (Fig. 1A). The tachycardia is not sustained because of block in the retrograde limb (that is, He-Ae block). Abbreviations as in Figure 1.

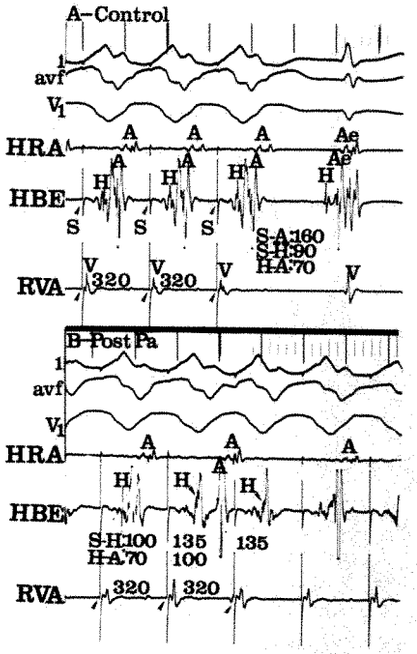


FIGURE 3. Case 1. Ventricular pacing during control study (**A**) and after administration of procainamide (**B**). **A**, ventricular pacing at a cycle length of 320 ms results in 1:1 V-A conduction. The S-H and H-A intervals measure 90 and 70 ms, respectively. **B**, ventricular pacing after procainamide (PA) at a similar cycle length as control results in a 3:2 V-A block. There is prolongation of both the S-H and H-A intervals after procainamide, but the block occurs between the H and A deflections (that is, the retrograde fast pathway). Abbreviations as in Figure 1.

After procainamide, the A-H interval during sinus rhythm measured 90 ms and the H-V interval 65 ms. Atrial pacing resulted in a smaller increase in A-H interval (90 to 130 ms) before the onset of A-V nodal Wenckebach block than that of the control period. Also, the length of the atrial pacing cycle that resulted in A-V nodal Wenckebach periodicity decreased compared with the control value (330 compared with 350 ms) (Table I). The last conducted beat of the Wenckebach sequence (Fig. 2) resulted in two QRS complexes due to simultaneous conduction in the anterograde fast (A-H = 120 ms) and anterograde slow (A-H′ = 460 ms) pathway and an echo response. The H′-Ae interval was 70 ms longer than the control value (H-Ae = 40 ms) (Fig. 1A). Also, the tachycardia was not sustained because of block in the retrograde fast pathway (that is, H-Ae block). During atrial premature stimulation, supraventricular tachycardia could not be induced because of inability to achieve a critical A_2-H_2 interval (Fig. 1B). The functional and the effective refractory periods of the anterograde fast pathway decreased (Table I) whereas that of the anterograde slow pathway could not be determined because of shortening of the effective refractory period of the anterograde fast pathway (less than 305 ms) and atrial refractoriness.

Ventricular pacing during control studies demonstrated 1:1 V-A conduction up to a pacing cycle length of 320 ms (Fig. 3A). After procainamide (Fig. 3B) at a similar ventricular pacing cycle length, 3:2 V-A block occurred because of failure in the retrograde fast pathway. There was prolongation of both S-H (retrograde His-Purkinje) and H-A (retrograde A-V nodal) intervals before block; but the block occurred between the retrograde His bundle deflection and the atrium.

During ventricular premature stimulation both S_2-H_2 and H_2-A_2 intervals increased after procainamide compared with

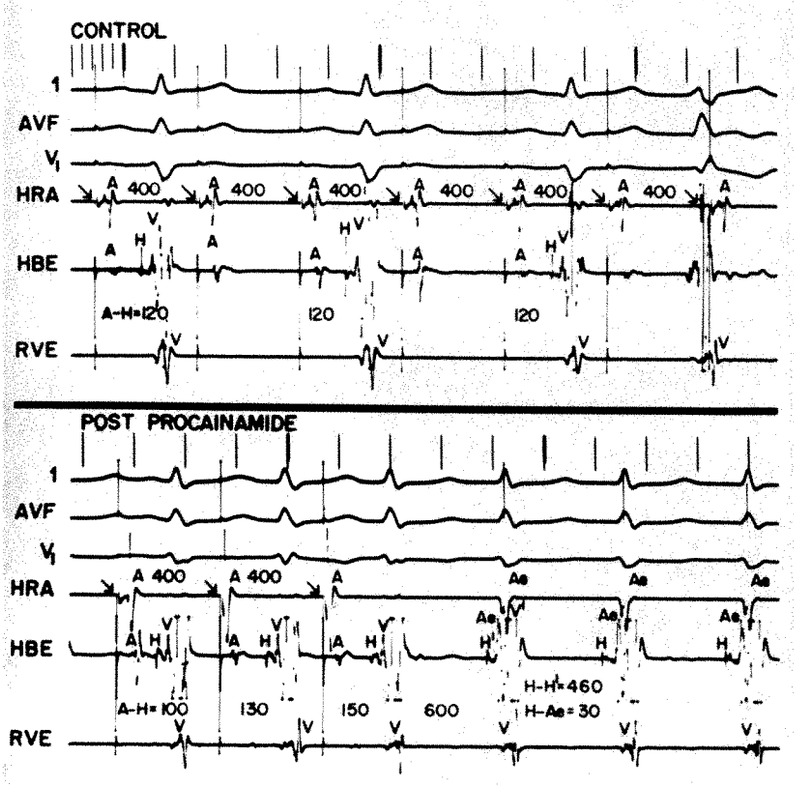


FIGURE 4. Case 2. Atrial pacing during control study and after administration of procainamide. **Upper panel,** atrial pacing during control period at a cycle length of 400 ms results in 2:1 A-V block. **Lower panel,** atrial pacing at a similar cycle length after administration of procainamide results in Wenckebach periodicity. The last paced beat of the Wenckebach sequence results in two QRS complexes due to simultaneous conduction in the anterograde fast (A-H = 150 ms) and the anterograde slow pathway (A-H′ = 600 ms) and a reentrant supraventricular tachycardia ensues.

control values, thus suggesting that the increase in the functional refractory period of the V-A conduction system (that is, the retrograde A_1-A_2) after procainamide was related to an increase in the functional refractory periods of both the His-Purkinje and retrograde A-V nodal systems (that is, the retrograde fast pathway).

Case 2: This was a 55 year old man with recurrent paroxysmal supraventricular tachycardia. Control conduction studies during sinus rhythm revealed an A-H interval of 75 ms and an H-V interval of 35 ms. Incremental atrial pacing resulted in progressive prolongation of the A-H interval (75 to 150 ms) before the occurrence of A-V nodal Wenckebach block. Neither atrial echoes nor supraventricular tachycardia resulted during atrial pacing-induced Wenckebach periodicity. Atrial premature stimulation revealed the presence of discontinuous A-V nodal curves with induction of a slow-fast tachycardia coincident with failure in the anterograde fast pathway. The critical A_2-H_2 delays required for induction of tachycardia ranged from 505 to 545 ms. The functional and effective refractory periods of the anterograde fast pathway measured 500 and 440 ms and that of the slow pathway 785 and 380 ms, respectively (Table I).

After procainamide, the A-H interval during sinus rhythm was 70 ms and the H-V interval 40 ms. In contrast to control studies when atrial pacing at a cycle length of 400 ms showed a 2:1 A-V nodal block (Fig. 4A), atrial pacing at a similar cycle length after procainamide resulted in A-V nodal Wenckebach periodicity. However, the last paced beat of the Wenckebach sequence (Fig. 4B) resulted in simultaneous conduction in both the anterograde fast (A-H-150 ms) and the anterograde slow (A-H′ = 600 ms) pathways and induction of a sustained tachycardia. As in Case 1, V-A conduction time and the functional refractory periods of the His-Purkinje and that of the V-A conduction system increased (Table II).

Case 3: This was a 72 year old man with recurrent paroxysmal supraventricular tachycardia. Control studies demonstrated an A-H interval of 75 ms and an H-V interval of 50 ms. Atrial pacing-induced A-V nodal Wenckebach periodicity resulted in a slow-fast tachycardia (Fig. 5A). Unlike the situation in Cases 1 and 2, atrial premature stimulation (cycle lengths of 600 and 500 ms) revealed a smooth A-V nodal curve with induction of tachycardia at a critical A_2-H_2 interval of 240 ms.

After procainamide, the A-H interval was 60 ms and the H-V interval 55 ms. Atrial pacing-induced A-V nodal Wenckebach periodicity (Fig. 5B) resulted in simultaneous anterograde fast (A-H = 110 ms) and anterograde slow (A-H′ = 410 ms) pathway conduction and an echo response. Supraventricular tachycardia could not be sustained because of block in the retrograde fast pathway (that is, H-Ae block). Atrial premature testing revealed a smooth A-V nodal curve as in the control study with initiation of single echoes that blocked within the retrograde fast pathway. The functional refractory period of the anterograde fast pathway decreased after procainamide and the effective refractory period of the fast pathway could not be attained (Table I).

As in Cases 1 and 2, V-A conduction time and the functional refractory period of the His-Purkinje and V-A conduction systems increased after procainamide (Table II).

Discussion

The electrophysiologic findings in our three patients indicate that the site of reentry was the region of the A-V node. Of considerable interest, however, was the observation of (1) simultaneous anterograde fast and slow pathway conduction resulting in a double ventricular response and initiation of a slow-fast echo or

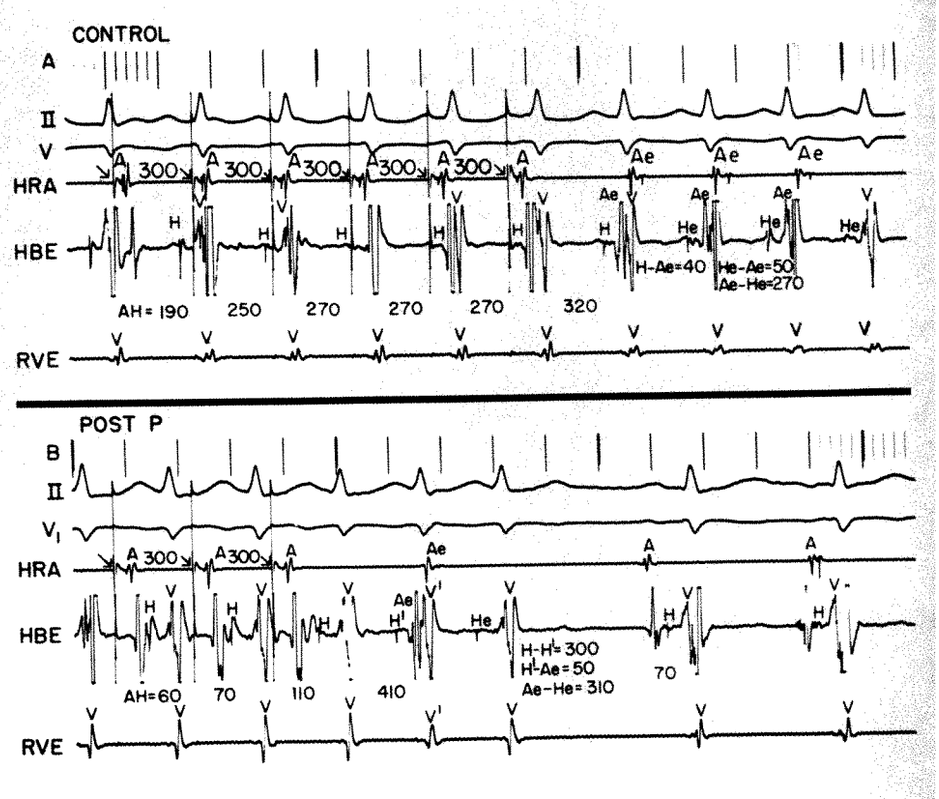


FIGURE 5. Case 3. Atrial pacing during control study (**A**) and after administration of procainamide (P) (**B**). **A**, atrial pacing at a cycle length of 300 ms results in Wenckebach periodicity with induction of a slow-fast supraventricular tachycardia. **B**, atrial pacing after procainamide (PA) at a similar cycle length also results in Wenckebach periodicity but the A-H interval is shorter than the control interval. Also, the last paced beat of a Wenckebach sequence results in a double ventricular response due to simultaneous conduction in the anterograde fast pathway (A-H = 110 ms) and anterograde slow pathway (A-H′ = 410 ms) and an echo response. The H′-Ae interval is 50 ms longer than during the control period (H-Ae = 40 ms). The tachycardia is nonsustained because of block in the retrograde fast pathway.

TABLE II

Retrograde Conduction and Refractory Periods (ms) Before and After Procainamide (P)

	Case 1		Case 2		Case 3	
	Control	After P	Control	After P	Control	After P
VCL for V-A block	300	320	350	400	300	320
V-A conduction system						
FRP	360	370	340	370	370	400
ERP	NA	NA	NA	NA	NA	NA
His-Purkinje system						
FRP	360	370	410	470	445	450
ERP	NA	NA	NA	NA	NA	NA
Ventricular myocardial ERP	230	260	240	250	250	260
VCL	600	600	600	600	600	600

ERP = effective refractory period; FRP = functional refractory period; V-A = ventriculoatrial; VCL = ventricular pacing cycle length.

tachycardia, or both, after procainamide, and (2) differential effects of procainamide on the anterograde fast and retrograde fast pathways.

Simultaneous Fast and Slow Pathway Conduction

Induction of a tachycardia in patients with paroxysmal A-V nodal reentrant tachycardia is characteristically associated with either (1) failure in anterograde fast pathway conduction with resulting anterograde conduction over the slow pathway and retrograde conduction over the anterograde fast pathway; reciprocation within the anterograde slow and fast pathways is believed to be the electrophysiologic basis of a reentrant tachycardia in patients demonstrating discontinuous A-V nodal curves (dual pathways)[4–6]; or (2) achievement of a critical A-V nodal conduction delay resulting in retrograde conduction over a fast retrograde pathway.[9] Reciprocation with a slow A-V nodal pathway and a fast retrograde pathway is believed to be the electrophysiologic basis of reentrant tachycardia in patients with smooth A-V nodal curves.[9] In contrast, simultaneous anterograde fast and slow pathway conduction resulting in a slow-fast tachycardia is exceedingly rare. Wu et al.[10] reported a single case with dual A-V nodal pathways in which a slow-fast tachycardia was initiated during simultaneous fast-slow pathway conduction during pacing-induced A-V nodal Wenckebach periodicity. They suggested that pacing-induced type I block in both pathways put these pathways "out of phase" so that the distal conducting system and ventricles were able to respond to both pathways. Recently Csapo[18] reported a single case with nonreentrant paroxysmal tachycardia with simultaneous fast-slow pathway conduction. He postulated that the effective refractory period of the His-Purkinje system was shorter than the difference between fast and slow pathway conduction so that single atrial beats could initiate two ventricular responses as a result of fast and slow pathway conduction. In contrast, dual ventricular responses from a single premature stimulus are not unusual in the Wolff-Parkinson-White syndrome,[19–21] in which the presence of two distinct insulated anatomic pathways (that is, the Kent bundle and the normal A-V nodal-His-Purkinje system pathway) make the phenomenon more readily explainable.

The exceedingly rare occurrence of simultaneous anterograde fast and slow pathway conduction in the region of the A-V node may be related to the following: (1) close proximity of the two functional or anatomic A-V nodal pathways; (2) incomplete insulation of the two pathways with crossover of the impulse to the slow pathway during anterograde fast pathway conduction so that the anterograde impulse traversing down the slow pathway finds the latter refractory at its caudal end and vice-versa; and (3) refractoriness of the His bundle after its excitation by the anterograde fast pathway.

Effect of procainamide: In our patients simultaneous fast and slow pathway conduction with induction of a slow-fast tachycardia was reproducibly observed only after the administration of procainamide and only during atrial pacing at rates that resulted in A-V nodal Wenckebach periodicity. Furthermore the stimulation sequences utilized during control studies were identical to those used after procainamide. This finding suggests that procainamide altered conduction and refractoriness of both pathways so that simultaneous conduction could occur resulting in a double ventricular response and a slow-fast tachycardia. Although the precise effects of procainamide that created the necessary milieu for simultaneous anterograde fast and slow pathway conduction is uncertain, the following three hypotheses can be offered (Fig. 6):

1. A greater enhancement of anterograde fast pathway conduction or shortening of refractoriness of the anterograde fast pathway relative to that of the anterograde slow pathway, or both, resulted in Wenckebach periodicity in both pathways. Thus, although Wenckebach periodicity was simultaneously occurring in the slow pathway, it was not manifested because of the faster anterograde fast pathway conduction. Only when the stimulator was turned off did conduction in the slow pathway become manifest resulting in a double ventricular response (Fig. 6A). Enhanced conduction within the anterograde pathway and a decrease in refractori-

ness after procainamide is supported by the observation of a smaller increase in the A-H interval before development of A-V nodal Wenckebach block compared with the control value, a shorter cycle length for Wenckebach periodicity compared with the control value and shortening of the functional and effective refractory periods of the anterograde fast pathway.

2. Complete insulation of the two pathways is produced by procainamide (Fig. 6B). However, if this hypothesis were true, then one would have expected simultaneous conduction during atrial premature stimulation.

3. Conduction shifts from the anterograde fast pathway to the anterograde slow pathway[18] (Fig. 6C). Although this seems a distinct possibility, the inability of the electrode catheter technique to assess the point of turnaround of the impulse within the A-V node (that is, the distal common pathway) makes this hypothesis difficult to prove or disprove.

The induction of an echo response through the fast pathway during simultaneous anterograde fast and slow pathway conduction may be related to (1) sufficient delay in the slow pathway enabling the anterograde fast pathway to recover excitability so that retrograde conduction could occur through the anterograde fast pathway, or (2) selective utilization of a retrograde fast pathway different from the anterograde fast pathway.

Differential Effects of Procainamide on Anterograde and Retrograde Fast Pathways

Effect on anterograde fast pathway: Procainamide demonstrated differential effects on the anterograde fast and retrograde fast pathways in all three patients. Enhanced conduction and decreased refractoriness of the anterograde fast pathway is supported by the following findings: (1) a relatively smaller decrease in the A-H interval before development of A-V nodal Wenckebach block, and (2) a decrease in both the functional and effective refractory periods of the anterograde fast pathway. In Case 1 the effective refractory period of the anterograde fast pathway could not be attained following procainamide and was probably less than the effective refractory period of the atrium. Also the inability to demonstrate a discontinuous A-V nodal curve after procainamide in this patient was obviously related to marked shortening of the effective refractory period of the anterograde fast pathway so that a discontinuous A-V nodal curve during control was converted to a smooth A-V nodal curve after administration of procainamide. In a previous study on the effects of procainamide in A-V nodal reentrant tachycardia Wu et al.[22] found that this drug had no significant effects on the anterograde fast pathway. However, their data indicate that procainamide decreased the effective refractory period of the fast pathway in four of eight patients in whom dual pathway curves were observed both during the control period and after administration of procainamide. Furthermore, in another four patients they could not assess the effective refractory period of the fast pathway because after procainamide dual pathway curves were converted to smooth A-V nodal curves. It is likely that the conversion of a dual pathway curve to a smooth curve was related to the shortening of the effective refractory period of the fast pathway, the attainment of which was limited by atrial refractoriness as in our Case 1. We were able to assess refractoriness of the anterograde slow pathway only in Patient 2, in whom procainamide decreased both the functional and effective refractory periods of the slow pathway. However, enhanced slow pathway conduction is suggested by shorter cycle lengths resulting in A-V nodal Wenckebach block. These effects of procainamide on the anterograde fast and slow pathways are in all likelihood related to the vagolytic effects of the drug.[23,24]

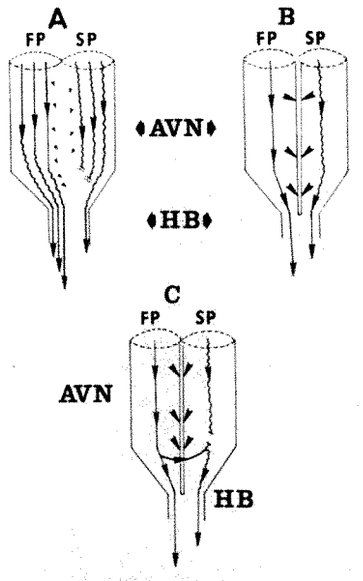


FIGURE 6. Schematic representation of the mechanisms for simultaneous anterograde fast (FP) and slow (SP) pathway conduction after procainamide. **A**, simultaneous Wenckebach periodicity within the fast and slow pathways. The first two impulses down the slow pathway are not manifest because of more rapid fast pathway conduction. However, the third impulse down the slow pathway becomes manifest after the third impulse down the fast pathway, but only when the stimulator is turned off. **B**, simultaneous conduction due to insulation of the fast and slow pathways. **C**, crossover of the impulse from the fast to the slow pathway during fast pathway conduction, resulting in a dual ventricular response. For further explanation see text. AVN = atrioventricular node; HB = His bundle.

Effect on retrograde fast pathway: In contrast to the effects of procainamide on the anterograde fast pathway, the drug had a depressant effect on the retrograde fast pathway, as suggested by the following: (1) the occurrence of V-A block at longer cycle lengths than control values; (2) lengthening of the functional refractory period of the retrograde fast pathway, as suggested by an increase in the functional refractory period of the V-A conduction system; and (3) inability to sustain tachycardia in Cases 1 and 3 because of block in the retrograde fast pathway. These effects of procainamide are probably related to its direct depressant effects on the retrograde fast pathway and are in agreement with the observations of Wu et al.[22]

Clinical implications: The diametically opposite effects of procainamide on the anterograde fast pathway (enhanced conduction and shortening of refractoriness) and retrograde fast pathway (depressed conduction and lengthening of refractoriness) have important implications. These include: (1) The retrograde fast pathway is physiologically and perhaps anatomically distinct from the anterograde fast pathway, and (2) the drug response of the retrograde fast pathway resembles that of Purkinje muscle whereas the response of the anterograde fast pathway resembles that of the A-V node. Previous studies on the effects of digitalis[7,9] and verapamil[25] on the retrograde fast pathway support these conclusions.

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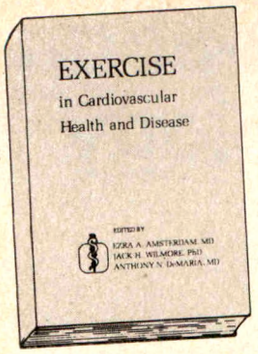
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WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Warnings). Aldactone should be used only in those conditions described under Indications. Unnecessary use of this drug should be avoided.

Indications: *Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.*

Contraindications: *Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.*

Warnings: *Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.*

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: *Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.*

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: *Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.*

Dosage and Administration

For primary hyperaldosteronism: *400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.*

For edema in adults: *Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.*

For edema in children: *Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.*

For essential hypertension: *Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.*

For hypokalemia: *25 to 100 mg. daily in divided doses.*

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☑ *Unlike other potassium-sparers, Aldactone specifically antagonizes aldosterone, thereby mitigating secondary volume buildup.*

For these reasons, Aldactone is a valuable adjunct in the treatment of CHF.

***Limitations to Consider**: Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and* Warnings *section of Aldactone prescribing information.)*

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the preceding page.

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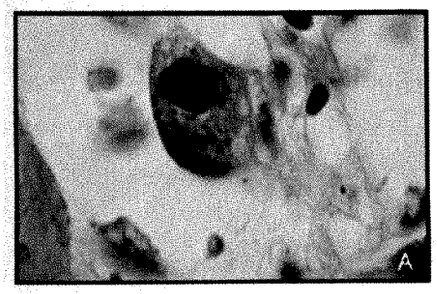
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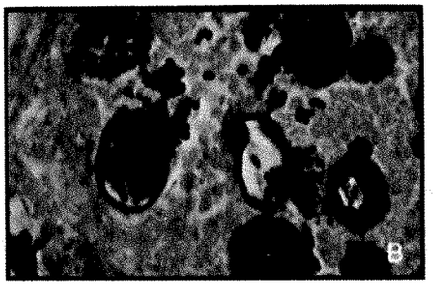
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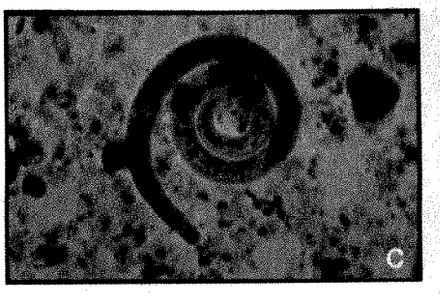
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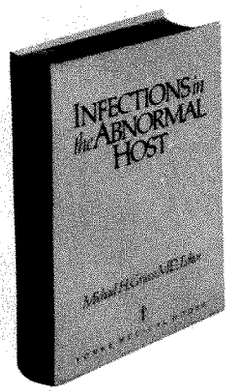
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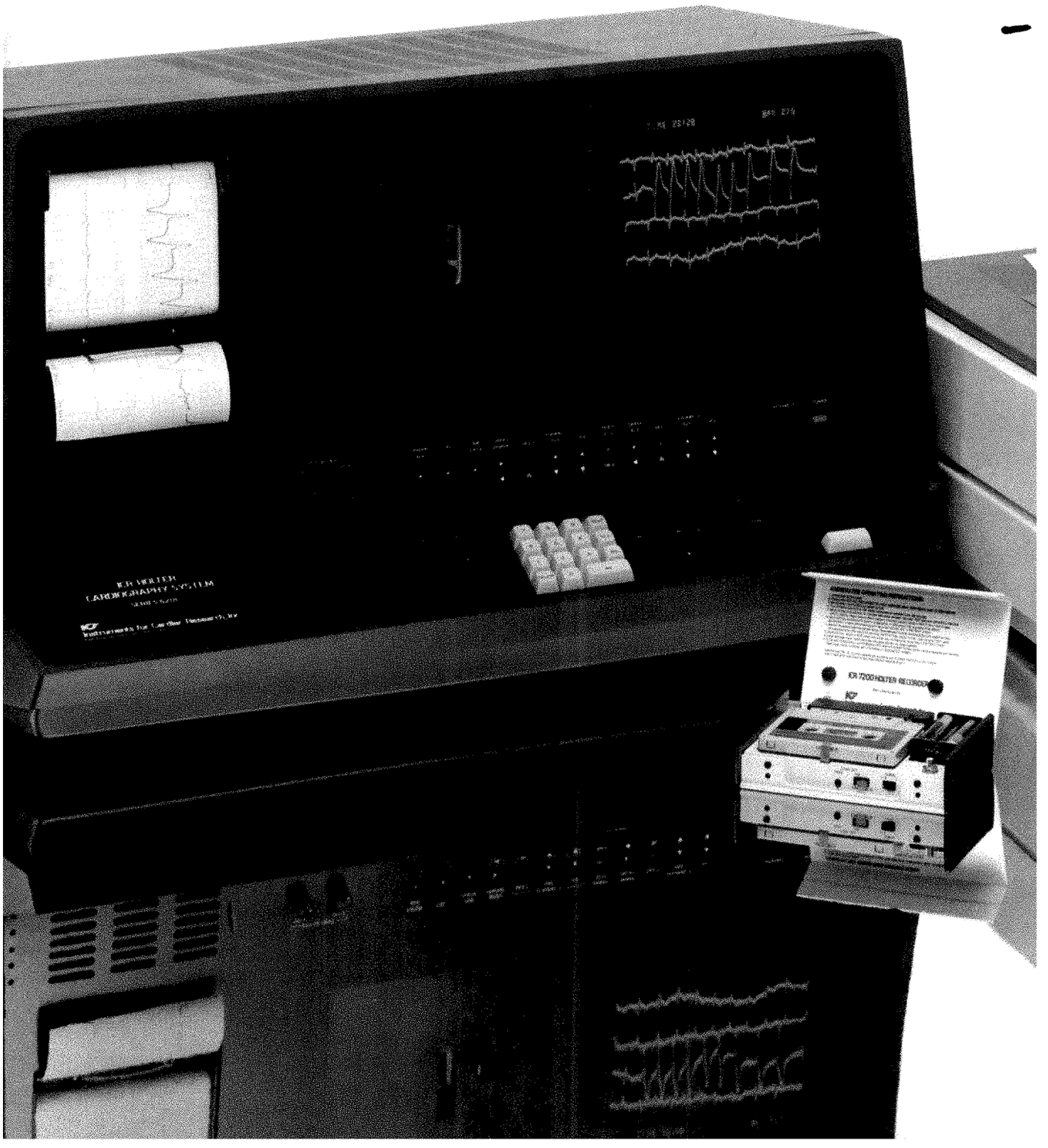
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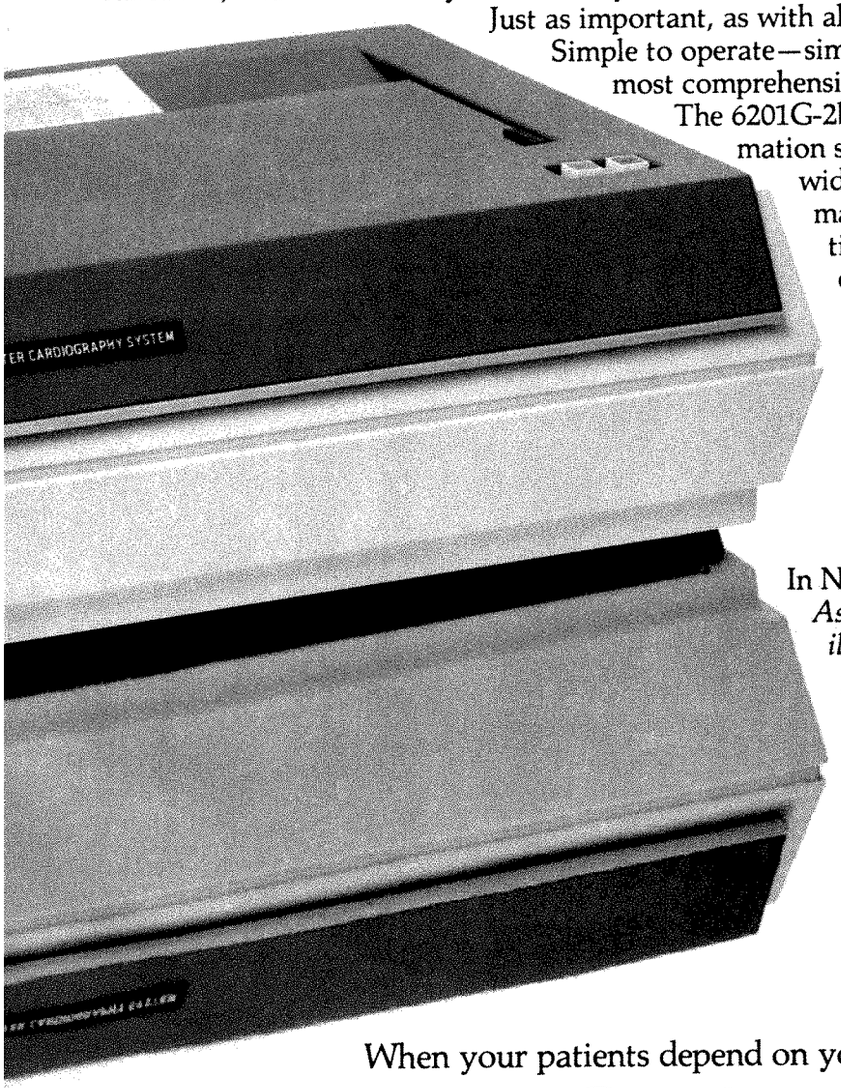
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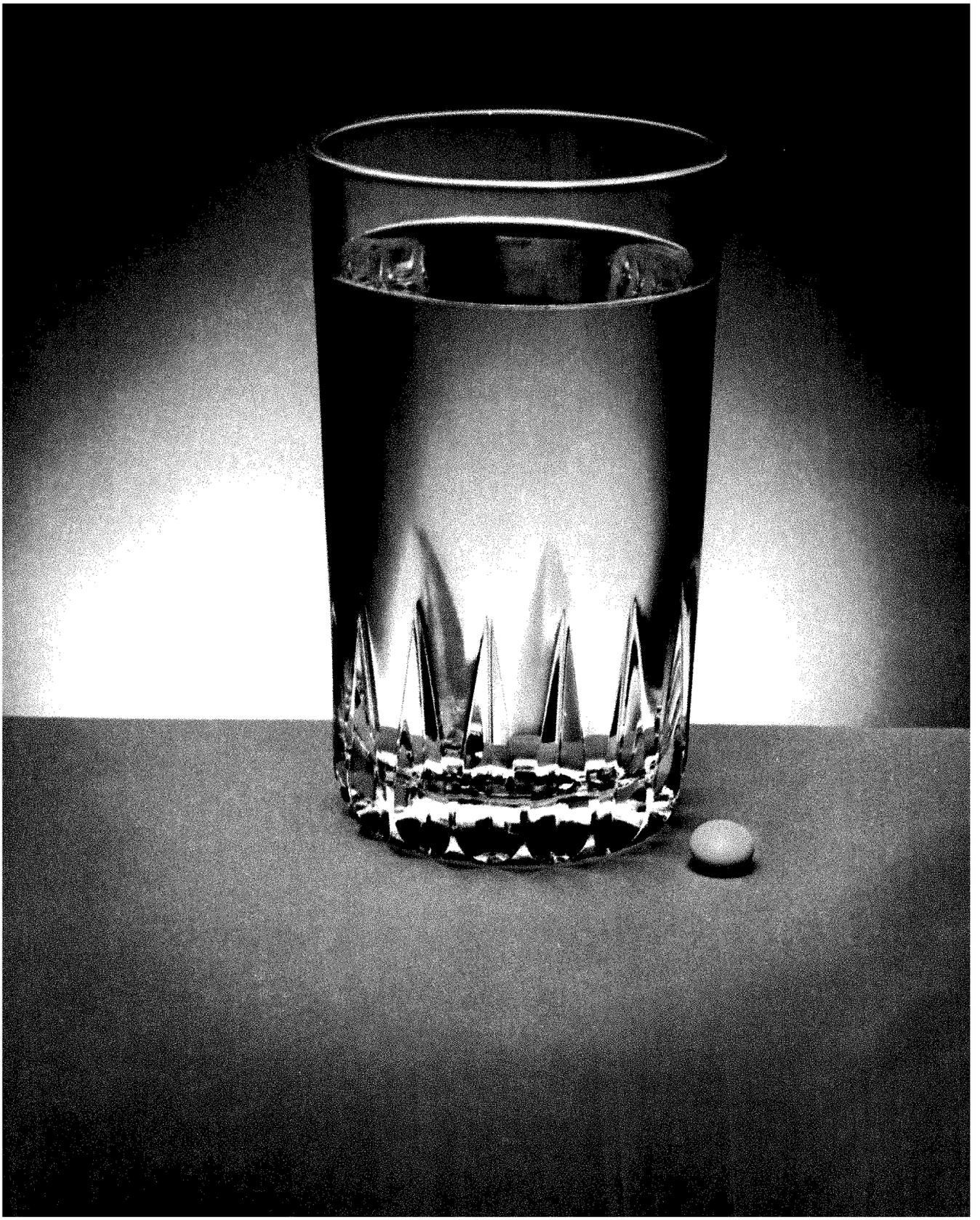
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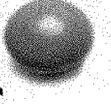
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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns. adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Cer Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visi Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—inde *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons v this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced b pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

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Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman the Department of Medicine, The University of Alabama in Birmi ham, and Physician-in-Chief, University of Alabama Hospitals.

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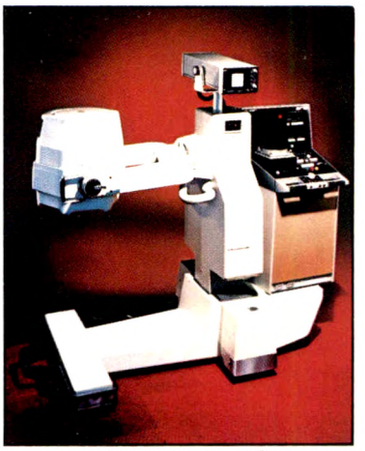
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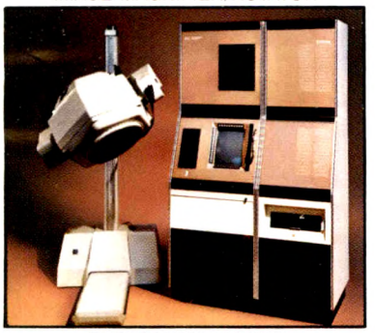
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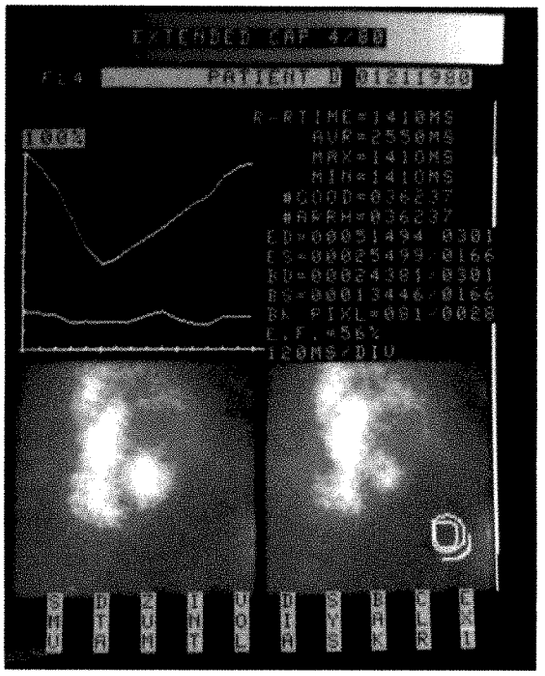
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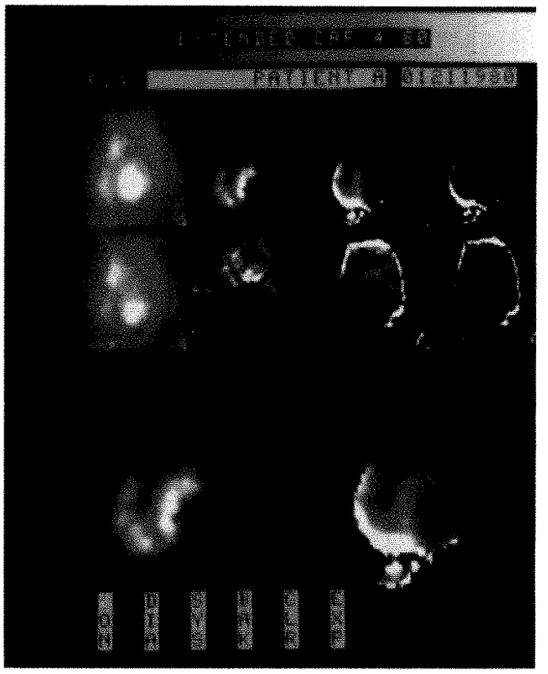
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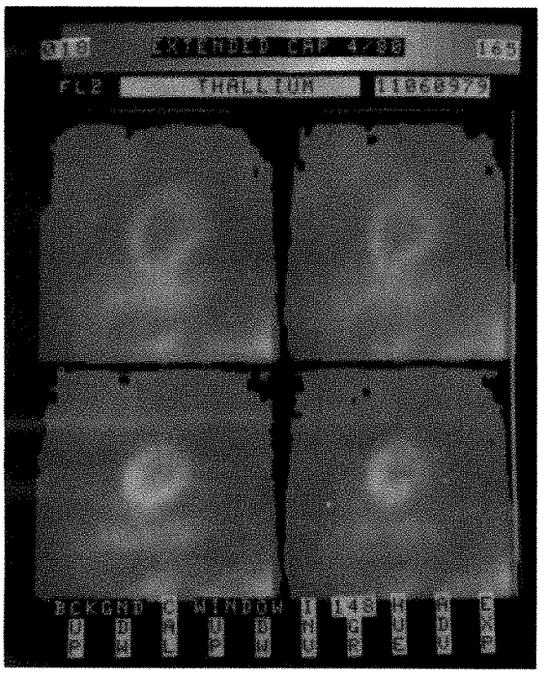
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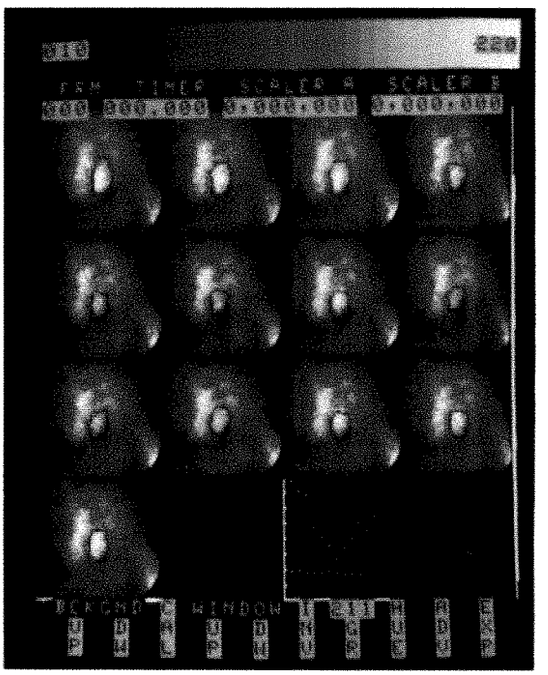


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Systemic Arterial Hypertension Associated With Cardiac Surgery

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ROBERT C. TARAZI, MD, FACC

Cleveland, Ohio

Significant hypertension can develop in 15 to 40 percent of patients undergoing various types of cardiac surgery. These hypertensive episodes can occur at almost any time before, during or after open or closed chest operations. The various hypertensions encountered in this context do not form a homogeneous entity; they are not due to the same causes and do not necessarily develop by the same mechanisms. Their frequency and seriousness have been demonstrated by reports from many centers: hence, the urgent need for accurate definition of their various types to allow correct identification and therapy. A classification based on well defined clinical events is therefore proposed and possible mechanisms for the more common types of hypertension are reviewed. Prophylactic measures include reassurance, attention to details of anesthesia and maintenance of preoperative antihypertensive therapy when indicated; for patients with coronary artery disease, preventive nitrate therapy as well as prompt attention to chest pain is essential. Both general and specific antihypertensive measures to control the more common types of hypertension complicating cardiac surgery are outlined.

Since its initial description in 1973,[1] hypertension has been increasingly recognized as a frequent complication of coronary bypass surgery[2–4] and has been reported to occur in 30 to 50 percent of cases.[1–3] The complication can be quite serious,[1,5,6] and the final outcome depends on the rapidity of diagnosis and early initiation of adequate therapy.[1,7] Apart from defining a specific problem, clinical studies of this syndrome have also created heightened sensitivity to hypertension in cardiac surgery and increased awareness that hypotension is not the only danger to be guarded against.[2,7]

As reports and studies from various centers rapidly increase, a more exact definition of the problem is needed to avoid confusion, especially because hypertension associated with cardiac surgery is not limited to coronary bypass grafting or to the postoperative period.[8–11] Pressor factors abound in the situation surrounding open heart surgery[1,11,12]; hence, hypertension may occur at different periods in relation to the procedure, as well as from various causes or mechanisms. The many mechanisms that can be involved in different circumstances are illustrated by current discussions about pathophysiologic characteristics and various approaches to therapy.[1–4,12–14] This multiplicity is hardly surprising because systemic arterial pressure is determined by a highly integrated cardiovascular control system. The multiple variables involved in this system[15] can all be affected by anesthesia, surgery and cardiopulmonary bypass: hence, the predisposition to potentially damaging hypotension or hypertension during major surgical interventions.

Classification

Serious hypertension can occur with any type of cardiac surgery and at practically any time, from the moment of wheeling the patient to the surgical unit to a few months after cardiac valve replacement.[3,7,16] A classification based on cause or specific mechanism would be both dif-

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ficult and premature because of the current controversy surrounding the subject and of the many factors involved. In contrast, a classification based on well defined clinical events such as timing in relation to surgery would allow an acceptable definition of the hypertension that is being considered and, thus, comparison of reports from different observers.

The hypertension occurring during endotracheal intubation or during cardiopulmonary bypass develops in a setting different from that which occurs during arousal from anesthesia. Grouping all these types of hypertension together, as some reports have done, would either prejudge the issue of causation or result in an unwieldly heterogenous entity (Table I).

The definition of levels considered as hypertensive episodes has varied among published reports. Estafanous et al.,[1] in their original description, defined a hypertensive episode as a rise in blood pressure to levels above 160/100 mm Hg in previously normotensive patients or an increase of more than 30 mm Hg (either systolic or diastolic) above preoperative levels in hypertensive patients. Elevations rapidly controlled with sedation or by increasing the level of anesthesia have been discounted in most studies[1–3]; this does not mean that they should not be attended to carefully.

Preoperative Acute Hypertension

Chaptal et al.[17] stressed the frequency of acute increases in arterial pressure in the preanesthetic period; Roberts et al.[2] found such increases in 15 percent of their patients. Obvious reasons for these changes include inadequate premedication, anxiety and discomfort from various interviews, injections or tests. More important, a sudden rise of pressure in patients with coronary insufficiency can precipitate angina pectoris and trigger a vicious cycle of hypertension and chest pain.[18,19] Adrenergic hyperactivity was documented by a shortened Q-S_2 interval in many patients before saphenous vein bypass grafting; this interval measured preoperatively was, in fact, significantly shorter in those who later had a perioperative infarction.[20] Premedication to provide adequate sedation and analgesia is obviously needed; the routine use of nitrites ("nitroglycerin paste") as a component of premedication might also help prevent a paroxysm of hypertension secondary to coronary insufficiency.

Role of preoperative antihypertensive agents: Of particular importance in this context is careful preoperative monitoring of arterial pressure. Hypertension can develop before the chest pain of coronary insufficiency.[18] Rapid increases in blood pressure could also be due to cessation of antihypertensive therapy before surgery.[21] Better knowledge of pharmacology and circulatory control mechanisms has modified that practice, which was the rule until the early 1960s[22]; each case and each drug must be considered in its own right. The tendency today would be to avoid cessation of antihypertensive therapy to prevent the burden of a rising pressure on the heart and atherosclerotic vessels.[22,23] Because newer antihypertensive agents have a much shorter duration of action than that of older drugs such as reserpine and guanethidine, the return of arterial pressure to hypertensive levels could occur rapidly. Moreover, "rebound" adrenergic hyperactivity has been described after abrupt cessation of clonidine[24] and propranolol[25]; the clinical findings are not restricted to an increase in pressure but include a recognized syndrome of restlessness, tachycardia and a slight flush suggestive of an autonomic crisis. In this situation the possible dangers to a patient with cardiac or coronary disease are obvious. The time has therefore come for a reevaluation of rules regarding beta adrenergic blockade and cardiac surgery. It is now our practice to maintain beta adrenergic blocking agents until the time of surgery. In our opinion, the advantages of decreased myocardial oxygen consumption obtained by controlling blood pressure and slowing heart rate outweigh the risk of possible hypotension during surgery, a risk that can easily be managed.

In summary, careful appraisal of antihypertensive therapy is an essential step in preparation for surgery. Rules regarding maintenance or discontinuance of treatment must be individualized with preference given, if possible, to continued control of arterial pressure by relatively short-acting agents that interfere as little as possible with baroreceptor reflexes.

TABLE I

Hypertension Associated With Cardiac Surgery

Preoperative
Anxiety situation, anginal crisis, and other incidences
Discontinuance of antihypertensive therapy
"Rebound" from beta blocking agents in patients with coronary artery disease
Intraoperative
Induction of anesthesia
Specific drugs
Hypertension due to tracheal intubation and nasopharyngeal, urethral or rectal manipulation
Precardiopulmonary bypass (during sternotomy and chest retraction)
Cardiopulmonary bypass
Postcardiopulmonary bypass (during surgery)
Postoperative
Early—within 2 hours
Obvious cause: hypoxia, hypercarbia, ventilatory difficulties, hypothermia shivering, arousal from anesthesia
With no obvious cause: after myocardial revascularization; less frequently after valve replacement; early (Sealy type I) hypertension after resection of aortic coarctation
Intermediate—12 to 36 hours after surgery: Sealy type II after repair of aortic coarctation
Late—weeks to months: after aortic valve replacement by homografts

Intraoperative Hypertension

Induction of anesthesia: This procedure constitutes one of the more serious threats to circulatory stability.[22] The dangers of hypotension and its management have been stressed in the past.[26–28] In that context, the relation of sympathetic activity of anesthetic agents, cardiac performance and vascular control is of particular importance. The contractility of the isolated heart is severely reduced by most anesthetic agents,[29] but this reduction is counterbalanced in intact organisms by reflex sympathetic activity.[22] Undue depression of adrenergic activity is undesirable in diseased hearts be-

ause they are more dependent than normal on this drive for adequate performance.[30] A case was therefore made for the discontinuance preoperatively of drugs such as some antihypertensive agents that could interfere with autonomic reflexes. However, hypertension during surgery can be equally threatening in patients with heart disease, particularly those with coronary artery disease. Although paroxysmal increases in pressure are not necessarily prevented by maintaining antihypertensive therapy, they might be exaggerated by its untimely discontinuance.[2,21] In that context, coronary artery disease adds another complication because of the potential imbalance between a restricted myocardial oxygen supply and the increasing demand secondary to a rising pressure.

Tracheal intubation: Severe intraoperative hypertensive episodes are particularly likely to occur at three periods: during intubation (Fig. 1), during median sternotomy and retraction of the chest wall and some time during or immediately after cardiopulmonary bypass. Induction of anesthesia by morphine sulfate[31] or the use of pancuronium bromide for muscle relaxation[32] can lead to undesirable tachycardia and an increase in arterial pressure in patients with coronary artery disease. However, a much more severe and frequent hypertension is associated with tracheal intubation. Stimulation of nerve endings in the nasopharynx by thermal probes and nasogastric tubes can lead to severe hypertension in any patient, especially in preoperatively hypertensive subjects when anesthesia is light and the stimulation prolonged. The increase in blood pressure is not usually prevented by previous antihypertensive therapy. Similar increases in pressure can also be seen on extubation.[33] These hypertensive crises can produce acute left ventricular dysfunction[22] and affect the outcome of cardiac surgery. Several protocols have been designated to minimize them. They include increasing the level of anesthesia and use of local anesthetic sprays, intravenous vasodilators, beta blocking agents and even stellate block.[34]

Sternotomy: During median sternotomy, acute hypertension was found to develop rather frequently in 47 percent in one series of 40 patients reported on by Chaptal et al.[17] and in 41 percent of 69 hypertensive episodes described by Roberts et al.[2] The increase in arterial pressure was usually associated with tachycardia, ST-T wave changes and, occasionally, multifocal ventricular premature complexes.[17] This initial elevation in pressure was associated with a later postoperative episode in 54 percent of one series.[2] The mechanisms of this hypertension have not yet been defined precisely although the clinical findings suggest sympathetic stimulation, possibly reflex in origin. The hypertensive response to sternotomy in human subjects contrasts sharply with the marked reduction in blood pressure seen on opening the chest wall in spontaneously hypertensive rats,[35] although not in rats with renal hypertension.[36] These differences in response, apparently to the same stimulus, underline the difficulty in extrapolating results from one cardiovascular setting to another.

Cardiopulmonary bypass: On initiation of cardiopulmonary bypass, mean arterial pressure usually decreases by as much as 45 percent but it begins to rise toward prebypass levels within a few minutes.[37] The reduction and subsequent increase in arterial pressure are not related to changes in cardiac output because these develop while the aorta is cross-clamped and the heart excluded from the circulation. Also, the changes in mean arterial pressure do not reflect the changes that occur in the pump output; the rise in arterial pressure is therefore mainly related to variations in peripheral vascular resistance. The cause and mechanisms of these variations have not been fully elucidated. Factors mentioned include dilating effects of priming solutions, histamine release, increase in antidiuretic hormone and alterations in circulating catecholamines.[37-39] Concerning the latter, in most reports the data have been analyzed in unifactorial terms rather than as part of a complex of interacting mechanisms.[40] In a situation entailing cross-clamping and manipulation of the aorta, activation of reflex pressor mechanisms[41] could be postulated. Less speculative are changes in circulating angiotensin II levels consequent to cardiopulmonary bypass.[4,42]

Taylor et al.[43] have shown that plasma angiotensin II levels were markedly higher during nonpulsatile bypass and that this increase could be attenuated by using pulsatile flow. Alterations in peripheral vascular resistance were said to correlate closely with changes in plasma angiotensin II; further, arterial pressure and vascular resistance decreased significantly after infusions of captopril.[43] The evidence appears quite impressive but it was derived only from observations or experiments in which mean arterial pressure was not increased.[42,43] The extension of these conclusions to hypertension was only inferential; despite the high levels of plasma angiotensin II reported, no actual hypertensive episode was described. That nonpulsatile flow can activate the renin-angiotensin system and increased angiotensin II can lead to marked vasoconstriction appear plausible; their casual relation to intraoperative hypertension has not yet been directly demonstrated.

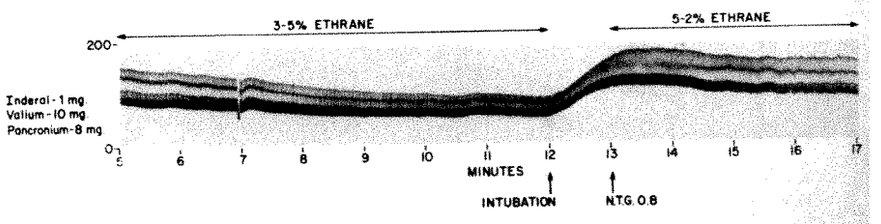


FIGURE 1. Hypertensive response to endotracheal intubation. N.T.G. = nitroglycerin.

Hypertensive episodes during cardiopulmonary bypass have not been infrequent in our experience; Roberts et al.[2] did not mention any in their series of 100 consecutive operations. When these episodes occurred the increase in pressure in our patients did not respond either to deepening the level of anesthesia or to reducing pump flow, but it was controlled by vasodilators. This increase in blood pressure did not correlate with the subsequent development of hypertension in the postoperative period.

Hypertension After Cardiac Surgery

Paroxysmal hypertension in the immediate postoperative period is a frequent and potentially dangerous condition. Many precipitating factors could be implicated: arousal from anesthesia, tracheal and nasopharyngeal manipulations, pain, hypothermia, shivering, poor ventilation and the use of pressor agents as well as the diminishing effects of antihypertensive medications. In addition, postoperative coronary insufficiency or myocardial infarction might increase blood pressure; signs of cardioadrenergic stimulation were particularly marked after coronary bypass in those patients who sustained a postoperative infarction.[20] Hypervolemia is often cited as a possible cause of postoperative hypertension. However, the relation of fluid overload to increased arterial pressure is more complex than the relation between container and content.[44] Compensatory neural mechanisms can adequately buffer sizable variations blood volume[45]; only in the functional absence of such reflexes or of renal excretory function will arterial pressure correlate directly with hypervolemia.[44,46] However, marked sympathetic reaction to hypovolemia could be an unrecognized cause of serious hypertension and impaired tissue perfusion.[47]

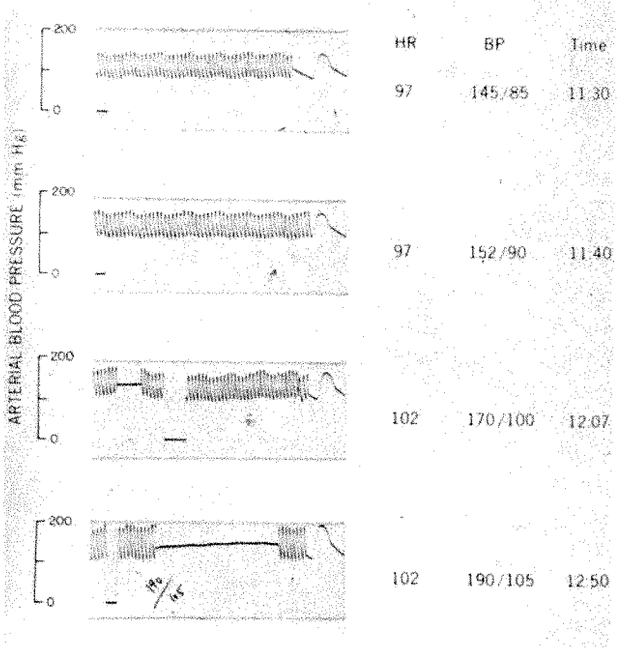


FIGURE 2. Hypertension after coronary bypass surgery. BP = blood pressure; HR = heart rate.

Early Types of Postoperative Hypertension

Postcoronary Bypass Hypertension

Since its original description in 1973,[1] this type of hypertension has been recognized as possibly the most common complication of coronary bypass surgery, occurring in 30 to 50 percent of patients.[2–4] A similar condition has also been seen after cardiac valve replacement, but the incidence rate is much smaller (8 to 10 percent).[1,10] The difference might be related to the brittleness and instability of blood pressure control in patients with coronary artery disease. Of particular importance are the reduced baroreceptor sensitivity[12] and frequent hypovolemia[48] in such patients.

The frequency of the condition and its serious implications[1–3,5] have stimulated a large number of studies; these have outlined a clinical syndrome with typical hemodynamic characteristics.[1,49] Generally agreed on are the early incidence of this hypertension in the first few hours postoperatively,[1–3] its paroxysmal course[1–3,12] and its association with mild tachycardia, increased peripheral resistance and an elevated mean rate of left ventricular ejection.[49] It has been reported as frequently among hypertensive patients as among previously normotensive subjects.[1–3]

Clinical description: The increase in arterial pressure occurs usually during the first 4 hours after operation both in patients already awake and in those still anesthetized. The blood pressure increases gradually but steadily (Fig. 2) despite adequate sedation and well controlled ventilation.[1,5] On clinical examination, we found no evidence of pallor, cyanosis or sweating, although the pressure may have occasionally exceeded preoperative levels by 60/35 mm Hg. This increase was not associated with any significant clinical sign except increased oozing and blood loss from the chest tube.[5] Despite the increase in pressure, there was no slowing of pulse rate; on the contrary, it tended to be slightly more rapid[12] with only occasional premature ventricular complexes[1]; ventricular fibrillation was reported in two patients.[17] Central venous and left atrial pressures usually remained within normal limits.[12,29]

A search for predisposing factors by several investigators did not produce any consistent results; findings were also mostly negative in our experience.[1,12] Most authors agree that the type of anesthetic agent, the duration of cardiopulmonary bypass and the distribution of coronary arterial lesions did not significantly influence the incidence of postoperative hypertension. Our impression was that this hypertension occurred more frequently among patients with well preserved myocardial function. This impression was strengthened by our experience with early systemic hypertension after cardiac valve replacement.[10] Hypertension appeared to develop somewhat more frequently after aortic valve replacement than after mitral valve replacement (12.1 versus 5.9 percent); none of the 18 patients who had double valve replacement had postoperative hypertension. This difference in incidence was attributed to

the difference in myocardial status among these groups.

Pathophysiology: The increase in blood pressure after coronary bypass surgery was related in all published reports[2,12,49,50] to an increase in total peripheral resistance. This conclusion was not based only on group averages; in our study the hemodynamic evolution after coronary surgery was described using each patient as his own control.[49] The change in hemodynamic pattern as pressure increased was the same in all patients, with no significant change in either cardiac output or central venous or left atrial pressure. These findings helped us to discount hypervolemia as a cause for this hypertension.[12] Two paradoxical findings were associated with the increase in pressure: (1) lack of slowing of heart rate, and (2) further elevation of the mean rate of left ventricular ejection. This hemodynamic pattern suggested an increased sympathetic drive that, in turn, helped to explain why cardiac output was not reduced despite the rapid increase in blood pressure.

Neural factors: The hypothesis of sympathetic stimulation was further supported by reports of statistically significant correlations between the increase in mean arterial pressure and elevations in plasma catecholamine levels.[2,12] However, these correlations were not very close, suggesting either the interplay of other factors or a lack of sufficient sensitivity of circulating catecholamines as an index of sympathetic activity.

We postulated as early as 1973 that the sympathetic overdrive was possibly related to activation of pressor reflexes from the heart, great vessels or coronary arteries. In favor of a reflex mechanism was the paroxysmal nature of the hypertension, its temporal relation to manipulation of the heart and its vessels and the absence of other obvious hemodynamic factors. The importance of pressor reflexes originating from the heart and great vessels has repeatedly been demonstrated[13,19,41,51–53]; Malliani and Brown[51] showed that depressor reflexes originating from the coronary arteries were mediated by vagal afferents in contrast to pressor reflexes that coursed through sympathetic afferents. A hypertensive chemoflex from the heart was related by James et al.[13] to a small serotonin-sensitive chemoreceptor in an area in which blood supply was derived from a special small branch of the left main coronary artery. This reflex is mediated by vagal afferents and its existence has not yet been proved in man.[13] Malliani et al.[52] reported that stretch of the thoracic aorta in cats led to reflex increases (mediated by sympathetic afferents) of arterial pressure and heart rate.

Our previous experience with stellate stimulation,[54] as well as the lack of any obvious predilection of postcoronary bypass hypertension for operations on any single coronary bed, suggested that of the various possible pressor reflexes, the more important in this context were those that involved sympathetic afferent fibers. We therefore elected to test the effect of unilateral stellate ganglion block in patients with hypertension after coronary bypass surgery. Both in our initial series of 27 patients[14] and in a subsequent larger group,[12] an effective unilateral block resulted in rapid and definitive normalization of arterial pressure in the vast majority of cases. The reduction in blood pressure was rapid, smooth and related to a decrease in systemic resistance with no evidence of diminished cardiac performance (Fig. 3).[14] These results were interpreted to indicate that the blood pressure response was probably due to interruption of afferent fibers coursing through or relaying in either stellate ganglion. If the blockade had acted mainly by interfering with efferent cardiac sympathetic drive, one would have expected a depression of cardiac output. This is what happens with acute beta adrenergic blockade; in such instances, cardiac output decreases but total peripheral resistance increases and blood pressure is left unchanged.[55] This pattern is obviously quite different from the immediate reduction in both arterial pressure and peripheral resistance produced by the unilateral stellate block. This widespread hemodynamic effect of a unilateral block suggests the interruption of a pressor reflex.

The success of stellate block does not mean that all cases of hypertension after coronary bypass surgery are due to pressor reflexes from sympathetic afferent fibers. Other causes of hypertension after cardiac surgery are known (Table I); even among those cases with no obvious cause, some hypertension might conceivably be due to activation of the hypertensive chemoflex.[13] A possible role for an activated renin-angiotensin system in some cases,[2] even if confirmed, does not necessarily contradict a "cardiac" origin for this hypertension because sympathetic stimulation is a potent cause of renin release.

Renin-angiotensin system: Reports by Roberts et al.[2] and other investigators[56–58] emphasized the pathogenetic importance of increased plasma renin activity in postcoronary bypass hypertension. Although this renin-angiotensin system can be activated during nonpulsatile cardiopulmonary bypass,[4,42,43] a definite relation of increased angiotensin II to postoperative

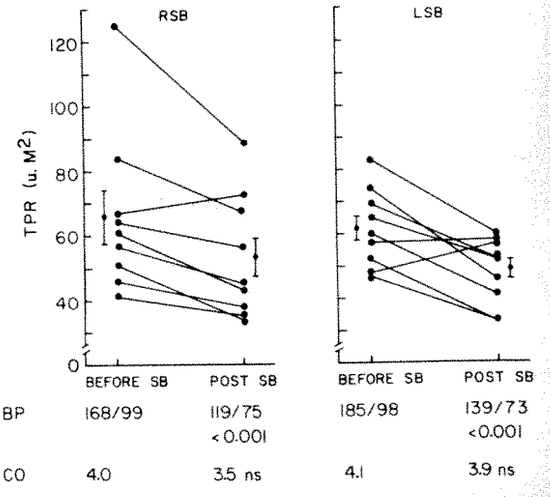


FIGURE 3. Effect of unilateral stellate block (SB) on hypertension after coronary bypass surgery. BP = blood pressure; CO = cardiac output; LSB = left stellate block; RSB = right stellate block; POST = after; TPR = total peripheral resistance.

ypertension has not, in our opinion, been demonstrated. Further, neither in our experience nor in that f others was it possible to document a particularly elvated plasma renin activity in patients in whom hyertension later developed after coronary bypass surery. No correlation was found during the postoperative eriod between changes in blood pressure and change ı plasma renin activity.[12] Converting enzyme inhibitors 'ere effective in control of hypertension after bypass ırgery,[59] but these results can hardly be considered nequivocal evidence of an angiotensinogenic causation. 'he very mechanisms by which these inhibitors de-'ease arterial pressure are themselves debated.[60]

arly Hypertension After Resection of ortic Coarctation

Hypertension after resection of coarctation of aorta as described by Sealy[61] in 1957. The increase in blood ressure occurs either early, immediately after surgery ype I), or 24 to 36 hours postoperatively (type II) 'intermediate postoperative hypertension"). The arly hypertension" was reported in more than 17 ercent of patients[61]; it lasts about 8 to 12 hours and sponds adequately to vasodilator therapy. In our exerience, its clinical characteristics are similar to those postmyocardial revascularization hypertension. The emodynamics of this type of hypertension were not udied because attention was mostly directed to the ore serious "hypertension type II."

Intermediate Hypertension

Hypertension after resection of aortic coarctaon: This type of hypertension (Sealy type II), which eveloped in 10 to 12 percent of patients, begins 36 to 3 hours after surgery; it is not related to the "early Sealy type I) hypertension" but its incidence and se-rity are related to both the tightness of the coarctation ıd the age of the patient.[61,62] The rise in pressure is ost pronounced in the diastolic levels and is usually companied by significant tachycardia; it is often mplicated by abdominal pain and signs and symms of an acute abdomen due to mesenteric endartitis.[62] The increase in pressure has been related to creased sympathetic activity consequent to reduction baroreceptor inhibition of vasomotor centers. After ccessful resection of the coarcted segment, the arterial essure decreases in the upper part of the body leading inactivation of the baroreceptors that had been acstomed to higher pressure levels. The release of mpathetic activity from tonic baroreceptor inhibition sults in a "vasoconstrictor storm" [63] with marked elation of blood pressure and heart rate. The mesenteric ssels that were used to the lower level of pressure evailing below the level of the coarctation are now ddenly exposed to severe hypertension, precipitating darteritis and vascular necrosis with consequent instinal ischemia and infarction. Clinical awareness of is syndrome and routine early prophylactic antihyrtensive agents have minimized the incidence of this mplication.

Late Hypertension

Aortic valve replacement by homograft: Layton et al.[16] reported in 1973 a type of late postoperative hypertension after aortic valve replacement by homograft. In their experience, this hypertension occurred in up to 50 percent of patients; in some cases the blood pressure began to increase early after surgery, but the incidence of hypertension gradually increased to involve more than half of their 116 patients 5 years after valve replacement. This incidence was much greater than that expected from general statistical considerations for this particular population. The development of hypertension was not related to preoperative blood pressure levels; however, it was more frequent in male than in female patients and in those who underwent surgery for aortic regurgitation than in those who had aortic stenosis. Neither the cause nor mechanisms of the increase in blood pressure were clear; what was significant was the high rate (40 percent) of homograft valve failure in patients with uncontrolled hypertension as compared with the 11 percent of failure in those who remained normotensive or whose blood pressure was adequately controlled.

Treatment

Whatever the causes and timing of hypertension, it is a serious complication for patients recovering from open heart surgery. The increase in pressure and in total peripheral resistance increases cardiac work and myocardial oxygen consumption. Previous studies[50,64] demonstrated that the endocardial viability ratio, as well as the ratio of diastolic to systolic pressure time indexes, was lower in patients who had postoperative hypertension than in those who remained normotensive. The decrease in these indexes means an increased susceptibility to subendocardial ischemia, which can be further aggravated by the anemia due to the hemodilution that is often used in heart surgery.[65] Hypertension also increases the risk of cerebrovascular accidents. The incidence and amount of postoperative bleeding in a previously heparinized patient are much greater during hypertension. It is evident, therefore, that every effort should be made to prevent, control and treat hypertension promptly and adequately during various stages of heart surgery.

Adequate treatment depends on correct diagnosis. Wide variations can and do occur in blood volume, total peripheral resistance, pulmonary vascular resistance, myocardial perfusion and contractility and heart rate, both during and after cardiac surgery. Hence, a correct diagnosis must be based on adequate monitoring and thoughtful interpretation of various indexes. These entail close follow-up (using properly calibrated equipment) of both pulmonary and systemic arterial pressures, as well as the filling pressure in the right heart chamber and, if possible, also in the left chambers. Determination of cardiac output and estimate of fluid balance are important in certain conditions. A rational choice of therapy is made easier by defining the mechanisms underlying the rise of arterial pressure at dif-

erent stages of surgery or of the postoperative pe-iod.

General Measures

Attention to details, thoughtful preparation of the patient and general measures to avoid pain and vasoconstriction are more important in preventing hypertension or in treating it than hasty use of antihypertensive agents. Prophylaxis begins long before surgery. In our opinion, antihypertensive therapy including beta adrenergic blocking agents should be continued until the time of surgery. Hypotension, whether or not it is related to antihypertensive therapy, can be averted by good monitoring, and we believe that in proper circumstances its risks are far less than the deleterious effects of uncontrolled hypertension. Although each case should be handled on its own merits it has been our impression that maintaining antihypertensive therapy is preferable. However, cessation of administration of diuretic drugs for 1 or 2 days may help avoid the risk of dehydration in patients who may have marginal renal function.

Hypertension due to pain and anxiety is minimized by adequate premedication with a strong analgesic agent (morphine sulfate) and an amnesic agent (scopolamine). During the postoperative period all patients should receive, in doses adjusted according to their hemodynamic status, sufficient analgesic and sedative agents every 2 hours for the first 48 hours and when required thereafter to ensure that they remain free of pain.[65]

Hypothermia and vasoconstriction do occur in both the operating room and the intensive care unit. When the the patient is rewarmed after hypothermic perfusion, body temperature may drift down again; hypothermia may also occur from exposure of the patient with open chest to the relatively low operating room temperature. Both nasopharyngeal and rectal temperatures must be closely monitored and all administered fluids warmed to 37° C. Warming blankets are used when needed to avoid the vasoconstriction provoked by cold.

Antihypertensive Agents

Peripheral vasodilators: Short-acting peripheral vasodilators that do not overstimulate the heart are the drugs of choice for treatment of hypertension during and after cardiac surgery. These vasodilators have a rapid onset of action and their dose can usually be titrated to achieve the desirable level of blood pressure. However, all vasodilators are not equivalent in their spectrum of action; those like diazoxide or hydralazine, which have little effect on veins may produce undue stimulation of the heart.[66] More appropriate to the conditions of cardiac surgery are vasodilators like sodium nitroprusside, which dilate veins as well as resistance vessels.[66]

Sodium nitroprusside: This vasodilator is the most consistently effective drug for management of hypertensive crises.[67] In our opinion, it remains the drug of choice for hypertension associated with acute coronary insufficiency and left ventricular impairment.[68–71] Left ventricular stroke work and filling pressure are decreased and left ventricular performance is enhanced.[69–71] Cardiac output could be increased, particularly when the left ventricular filling pressure is initially high and left ventricular function impaired; when left ventricular filling pressure is normal or low, cardiac output might be decreased to a variable extent. Similarly, heart rate is increased in subjects without heart disease but it is not significantly altered in those with cardiac decompensation.[69]

Nitroglycerin: For the last 10 years we have used different preparations of nitroglycerin perioperatively in open heart surgery.[72] It is a peripheral vasodilator for both resistance and capacitance vessels[73] with beneficial effects on the coronary circulation; in cardiac surgery it has proved useful as a short-acting hypotensive agent.

We have utilized nitroglycerin ointment (2 percent) in our routine premedication for all patients undergoing open heart surgery. Its effect begins 20 to 30 minutes after application and may last up to 3 hours[74]; patients are advised not to stand up after its administration, to prevent orthostatic hypotension. It is used to reduce preoperative angina pectoris and consequent reflex increases in blood pressure; moreover, its routine use may decrease the incidence and degree of the hypertension that complicates endotracheal intubation. For actual angina at any stage before induction, *sublingual nitroglycerin* is given as needed. It is also given in the postoperative period every 2 hours during the first 48 hours to all patients with coronary artery disease to minimize the incidence of the pain and hypertension that can result from coronary insufficiency.[18] However, as a more direct hypotensive agent, we have used *intravenous nitroglycerin* as an alternative to sodium nitroprusside when hypertension occurs during cardiac surgery. Because of its venodilating effect and its effect on the pulmonary circulation we believe that it is the drug of choice for the hypertension associated with right ventricular dysfunction or with increased pulmonary vascular resistance.

Diazoxide: Diazoxide and other predominantly arteriolar vasodilators greatly increase cardiac output and may result in hyperkinetic pulmonary hypertension, particularly in patients with diminished left ventricular function or compliance.[66] Hence, these vasodilators may be undesirable in patients with long-standing hypertension, after open heart surgery and in cases of fixed obstruction to pulmonary venous flow (mitral stenosis).[75]

Beta adrenergic blocking agents: In patients with marked tachycardia, particularly in association with ischemic S-T segment changes, intravenous propranolol can be used in the early stages of surgery. In this situation, slowing of the heart rate can be associated with some reduction in arterial pressure, especially the systolic level. However, because of its depressing effect on myocardial contractility and its relatively delayed hypotensive action,[76] propranolol is not recommended for postoperative hypertension.

Specific Measures

Whenever the exact mechanism or cause of the hypertensive episode is known, the best treatment is specific correction of the abnormality, if possible. Every effort must be spent toward ensuring that the increase in pressure is not related to a correctable cause such as poor oxygenation, asynchrony with the ventilator or fluid overload. In all such cases, correction of the cause will lead to cure of the hypertension. In other instances, the best treatment is anticipation of some particularly frequent types of hypertension. Finally, some specific measures have been recently developed to deal with particular forms of hypertension.

Hypertension related to tracheal and nasopharyngeal manipulation: The pressor response to tracheal intubation is particularly exaggerated in preoperatively hypertensive patients[77] and whenever the stimuation is prolonged.[78] Maintenance of antihypertensive therapy might help reduce the severity of the increase in pressure. Strengthening the level of anesthesia with use of a strong inhalational agent such as halothane might minimize the pressor response in some patients; however, short-acting antihypertensive drugs administered seconds before intubation have also been used successfully including alpha adrenergic blocking agents (phentolamine)[79] and vasodilators (intravenous bolus injection of sodium nitroprusside, 1 to 3 μg/kg body weight).[80] However, too rapid a decrease in blood pressure before intubation may have a deleterious effect, especially in hypertensive or atherosclerotic patients.[77] However, in our experience ensuring the smoothness and rapidity of intubation is the most successful means of preventing or reducing an increase in blood pressure.

Unilateral stellate block: Unilateral stellate ganglion blockade was effective in our experience[12] for rapid normalization of the elevated blood pressure in a large number of patients with hypertension after myocardial revascularization (Fig. 3) as well as in those with a hypertensive episode immediately after heart valve replacement. We have even found stellate block to be effective after large doses of peripheral vasodilators failed to control adequately the paroxysmal increase in pressure. However, unless this blockade is performed with great care by physicians trained in its use, the incidence of its success rate can be quite low and, more important, can be complicated by pneumothorax, hemothorax or nerve injury.[81] Bilateral stellate block is dangerous because of the possibility of undue cardiac depression.

Angiotensin II antagonists and converting enzyme inhibitors: These drugs, which interfere at different levels with the renin-angiotensin cascade, have been shown to reduce blood pressure very effectively when circulating angiotensin II levels are high. Most agents reduce peripheral resistance without significantly changing cardiac index, an effect similar to that produced by vasodilators acting at both the arteriolar and venular levels.[59,82] No significant tachycardia has been noted with their use; the heart rate remained remarkably stable despite marked reduction of blood pressure in hypertensive patients.[82–84] Because of these favorable hemodynamic characteristics these drugs may be particularly useful in hypertensive patients with heart disease, and have been tried successfully in the treatment of hypertension after myocardial revascularization.[59] However, both classes of drugs are still investigational; currently, only the angiotensin antagonists (saralasin) and teprotide can be given intravenously.

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election of Angina-Free Patients With Severe eft Ventricular Dysfunction for Myocardial Revascularization

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Stress thallium-201 myocardial imaging was used in two angina-free patients with severe congestive heart failure to identify clinically silent areas of ischemic myocardium and to distinguish between scar and reversibly ischemic myocardium as a cause for akinesia of left ventricular wall segments. Subsequent myocardial revascularization in these patients led to considerable improvement in their clinical state and findings in postoperative nuclear scans. Thus, stress myocardial imaging may be useful in selecting patients with severe left ventricular failure but no angina pectoris for myocardial revascularization.

Congestive heart failure secondary to left ventricular dysfunction from diffuse coronary artery disease is generally considered to be a relative contraindication to myocardial revascularization, particularly when it occurs in the absence of angina pectoris. However, patients are occasionally encountered with congestive heart failure due to known coronary artery disease who have no angina, but in whom there may be reason to suspect that clinically unrecognized ischemia may be contributing importantly to left ventricular dysfunction. Left ventricular angiography alone does not distinguish scarred myocardium from viable myocardium that is akinetic because of severe ischemia. Stress myocardial imaging with thallium-201 can differentiate viable myocardium from scar and therefore ought to be useful in selecting for revascularization patients with poor left ventricular function.

Two patients with severe coronary artery disease are described whose only clinical manifestation was congestive heart failure. Both patients had had multiple myocardial infarctions and had been considered for coronary revascularization elsewhere. Surgery was not advised on the basis of poor ventricular function and lack of angina pectoris. Both patients underwent thallium-201 exercise imaging of the myocardium, which revealed extensive areas of reversibly ischemic akinetic myocardium. On the basis of these findings myocardial revascularization was performed and resulted in considerable improvement in the condition of both patients.

Case Reports

Case 1

A 68 year old retired government worker presented to the Massachusetts General Hospital for evaluation of increasing congestive heart failure. The pa-

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tient, who smoked 80 pack-years of cigarettes and had a 2 year history of diabetes mellitus of adult onset, had had two myocardial infarctions, one in 1966 and the second in 1977. During both infarctions he had had severe dyspnea and diaphoresis but no chest pain. In October 1978, he was admitted elsewhere for cardiac evaluation because of increasing symptoms of congestive heart failure. He was unable to walk up one flight of stairs or a quarter of a mile on flat ground without becoming severely short of breath. He denied any angina pectoris.

Angiographic findings: Cardiac catheterization before admission documented a left ventricular end-diastolic pressure of 36 mm Hg, which increased to 41 mm Hg after angiography, a pulmonary arterial pressure of 48/27 mm Hg and a cardiac index of 1.6 liters/min per m^2. Coronary cineangiography demonstrated total occlusion of the right coronary artery and high grade obstructive lesions of the left circumflex coronary artery and of the left anterior descending coronary artery and its first diagonal branch. Left ventriculography demonstrated anteroapical akinesia and otherwise generalized severe hypokinesia; left ventricular ejection fraction was estimated as 15 percent. Because of the patient's severe left ventricular dysfunction and lack of angina pectoris, he was not considered a suitable candidate for coronary bypass surgery.

Cardiac examination: He was admitted for the first time to the Massachusetts General Hospital in January 1979 because of symptoms of increasing left-sided congestive heart failure. Physical examination revealed a man in moderate respiratory distress. Blood pressure was 160/90 mm Hg, the pulse rate was 120/min, and respirations were 28/min and somewhat labored. Jugular venous pressure was increased to the angle of the jaw at 90°, but there was no peripheral edema. There were rales at both lung bases. Cardiac examination showed a prominent left ventricular impulse palpable in the sixth intercostal space in the anterior axillary line. There was a very prominent summation gallop and a grade 2/6 apical systolic murmur. There were no pulses below the femoral arteries bilaterally. The chest roentgenogram showed cardiac enlargement with interstitial pulmonary edema. The electrocardiogram revealed evidence of inferior and anteroseptal scars and left ventricular hypertrophy.

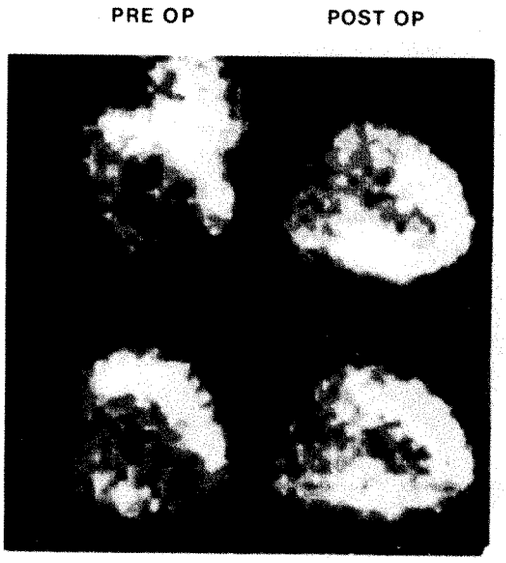


FIGURE 1. Case 1. Initial (INIT.) and delayed exercise thallium-201 imaging studies in the anterior (ANT) projection both before (PRE OP) and after (POST OP) coronary bypass graft surgery. The initial preoperative image shows a large defect involving the inferior and apical segments. In the delayed study the inferior wall demonstrates substantial thallium-201 fill in, and the apical defect persists. These findings suggest that despite the akinesia manifested on left ventricular cineangiography and gated blood pool scanning, the inferior wall is viable. In addition, the initial preoperative scan demonstrates increased lung activity that disappears in the delayed scan, suggesting that transient left ventricular failure was present at the time of the thallium injection. In the postoperative study, thallium-201 activity distribution appears normal, and lung activity is no longer evident.

Radionuclear imaging: After improvement in the patient's clinical status after diuresis and weight loss of 4.5 kg, a gated cardiac blood pool scan demonstrated a severely depressed left ventricular ejection fraction of 15 percent. The right ventricle contracted well. An exercise thallium stress test revealed areas of septal and inferoapical reversible ischemia (Fig. 1).

Cardiac surgery: In March 1979, saphenous vein aortocoronary bypass grafts were constructed to the left anterior descending, diagonal, circumflex marginal and posterior descending coronary arteries. At operation, the left ventricle was found to be markedly enlarged but without localized evidence of transmural myocardial infarction. The patient's pulmonary capillary wedge pressure before the institution of cardiopulmonary bypass was 28 mm Hg. He was weaned from cardiopulmonary bypass with a left atrial pressure of 14 mm Hg without any medications. The following morning the patient had a blood pressure of 130/70 mm Hg, a pulse rate of 95/min, a left atrial pressure of 11 mm Hg and a cardiac index of 2.4 liters/min per m^2. The rest of the patient's postoperative course was uneventful, and he was discharged to his home on the 18th postoperative day.

Postoperative course: A second gated cardiac blood pool scan performed 7 weeks after operation revealed an ejection fraction of 27 percent. An exercise thallium scan demonstrated more homogeneous distribution of the isotope throughout the left ventricular myocardium with activity present in the septum and inferior wall in the initial as well as in the delayed study (Fig. 1). Eight months postoperatively the patient is doing well and is limited only by lower limb claudication.

Case 2

A 40 year old mechanic was referred to the Massachusetts General Hospital for evaluation of increasing shortness of breath. The patient, previously a heavy smoker, had a posterolateral myocardial infarction in August 1977. He did well until September 1978, when he had an anteroseptal myocardial infarction. His second infarction was complicated by mild congestive heart failure. Six weeks after his second infarction he had 3 nights of paroxysmal nocturnal dyspnea. Evaluation at that time revealed a new murmur of mitral insufficiency.

Previous angiographic findings: During evaluation elsewhere the patient complained of fatigue, exertional dyspnea and weight loss but denied any angina pectoris or peripheral edema. At cardiac catheterization the following pressures were measured (in mm Hg): aortic 86/62, left ventricular 85/35, pulmonary arterial 53/26 (mean 32), pulmonary capillary wedge 36 (with V waves to 50), right ventricular 57/17 and right atrial 9. The cardiac index was 1.7 liters/min per m^2. Coronary arteriography revealed a normal nondominant right coronary artery and significant stenoses of the left

nterior descending, the first large diagonal and the circumflex narginal coronary arteries. Left ventriculography revealed a large anteroapical akinetic area with otherwise generalized evere hypokinesia. There was considerable mitral regurgiation, and the ejection fraction was estimated to be 12 to 15 ercent. Because of the patient's severe left ventricular failure ithout angina pectoris, he was thought not to be a suitable andidate for surgery. Subsequently, he did poorly and had vidence of right-sided failure with ascites and peripheral dema. His diuretic dosage was increased, and he was referred o the Massachusetts General Hospital.

Cardiac findings: On admission in February 1979, he was ound to be moderately dyspneic with a blood pressure of 0/80 mm Hg and a regular pulse (rate 70/min). His heart was narkedly enlarged and there was a diffuse left ventricular mpulse. There were S_3 and S_4 gallops and a grade 3/6 systolic murmur of mitral regurgitation. The electrocardiogram on dmission revealed sinus rhythm with evidence of old inferoposterior and anterior infarctions. The admission chest oentgenogram demonstrated marked cardiomegaly with mild nterstitial edema and left atrial enlargement.

A thallium stress test revealed reversibly ischemic segments in the interventricular septum and the high anterior wall of the heart with a large scar in the inferoapical wall (Fig. 2).

Cardiac surgery: At operation in February 1979, there was massive enlargement of both the left ventricle and right-sided chambers. Saphenous vein aortocoronary bypass grafts were constructed to the diagonal, left anterior descending and circumflex marginal coronary arteries. Two akinetic scarred segments were resected, a large area of the posterior wall of the heart measuring 4 by 13 cm and an area between the left anterior descending and diagonal coronary arteries at the apex measuring 3 by 5 cm. The mitral valve was excised and replaced with a 33 Hancock porcine xenograft valve. The patient was weaned from cardiopulmonary bypass with atrial pacing, with a systolic blood pressure of 130 mm Hg and a left atrial mean pressure of 16 mm Hg after infusion of a small amount of nitroprusside and dopamine.

Postoperative course: Some right ventricular failure resolved in the early postoperative period with a steady increase in the cardiac index. By the 4th postoperative day the patient had a blood pressure of 110/70 mm Hg, a pulse rate of 100, a left atrial pressure of 14 mm Hg and a cardiac index of 2.5 liters/min per m^2 without pressor support. His subsequent postoperative course was one of steady improvement. He was discharged home on the 14th postoperative day.

A second gated cardiac blood pool scan performed 13 months after operation revealed an ejection fraction of 33 percent. A thallium exercise scan showed normal septal, anterior and high lateral wall uptake with a persistent defect in the inferoapical wall that was smaller than that seen preoperatively. Thirteen months postoperatively the patient is very active and has only mild fatigue on exertion.

Discussion

These two cases demonstrate the difficulty in selecting for myocardial revascularization those patients who have silent myocardial ischemia. In both patients the problem was accentuated by the presence of congestive heart failure and by the difficulty in assessing the role that reversible ischemia might have played in its origin.

Angina pectoris versus left ventricular heart failure as a clinical marker of ischemia: Because angina pectoris is a specific clinical marker of myocardial ischemia, angina has become almost synonymous with the clinical presentation of coronary artery disease.[1,2] However, the sensitivity of angina as a clinical marker of severe coronary artery disease is probably very low. Various studies in the past have examined the incidence of prodromal angina pectoris before myo-

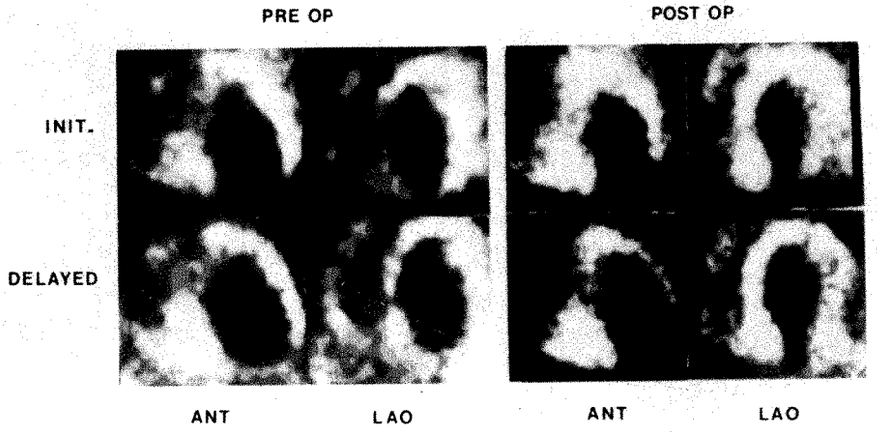


FIGURE 2. Case 2. Anterior (ANT) and 50° left anterior oblique (LAO) exercise thallium-201 myocardial imaging studies before (PRE OP) and after (POST OP) coronary bypass graft surgery. Initial (INIT.) and 2 hour delayed images are displayed with the initial scan in the **top row** and delayed images in the **bottom row.** The preoperative study demonstrates large initial defects in the inferior and apical segments in the anterior view and inferoapical and septal segments in the left anterior oblique view. All of these defects tended to be filled in, at least partially, in the delayed study. The postoperative study demonstrates only persistent defects in the inferoapical segment, which appear somewhat smaller than those in the preoperative study. The septum and high anterolateral wall appear to have improved perfusion in the postoperative study. Increased lung activity is present initally both preoperatively and postoperatively, a finding consistent with exercise-induced left ventricular failure. This lung activity can be seen in the **upper right corner** of each initial anterior image; it is less impressive in the postoperative study.

cardial infarction,[3–8] including a recent report[9] in which 48 percent of 577 patients presenting to the hospital with acute myocardial infarction had no prior history of angina pectoris. For these patients the myocardial infarction itself was the initial manifestation of clinically severe coronary artery disease. Other clinical presentations of coronary artery disease include functional mitral insufficiency, atrial and ventricular arrhythmias, congestive heart failure and atypical pain and dyspnea syndromes that have often been grouped under the term "anginal equivalents." In a broader sense it might be better to group these symptoms, as well as angina itself, under the term "ischemic equivalents of coronary artery disease."

Nevertheless, for most physicians angina pectoris remains a mandatory clinical correlate to anatomic disease as an indication for bypass surgery, and medically refractory angina pectoris is still the principal indication for myocardial revascularization. However, data[10–12] have recently appeared on surgical therapy for "asymptomic" patients (that is, patients without angina pectoris.) Our two cases support the view that it is not appropriate to exclude patients from consideration for myocardial revascularization purely on the basis of the absence of angina pectoris.[13]

Early surgical series[14,15] documented a small therapeutic benefit and a high operative mortality rate for myocardial revascularization in patients with severe left ventricular dysfunction. Most of the patients in those series had angina pectoris. More recent studies[16–18] have shown improved results in similar patients and hospital mortality rates of approximately 10 percent. Because it is difficult with left ventricular angiography to differentiate between reversible and irreversible left ventricular failure associated with ischemic heart disease, few surgeons feel comfortable in performing myocardial revascularization in patients with profound left ventricular dysfunction who do not also have significant angina pectoris.

Radionuclear myocardial imaging to detect ischemia in absence of angina: Thus, given that the absence of angina pectoris does not preclude life-threatening coronary artery disease in many patients and given the inability of left ventricular angiography to differentiate between left ventricular scar and segments that are akinetic because of ischemia, other methods have been used to try to verify the presence of myocardial ischemia and quantify its severity. The most widely applied of these methods is exercise electrocardiography. The reliability and specificity of exercise stress testing in asymptomatic patients have been reported to be quite low.[19] The addition of stress myocardial imaging with thallium-201 has enhanced the diagnostic accuracy of the electrocardiogram for the detection of coronary artery disease.[20,21] Some investigators[22,23] have reported radioactive microsphere distribution as a technique for identifying ischemic myocardium. In our patients we utilized myocardial imaging with thallium-201 both to identify myocardial ischemia that is not clinically evident and to differentiate between reversibly ischemic and irreversibly scarred myocardium.

Previous reports[20] indicate that serial imaging after a single dose of thallium-201 can differentiate between reversibly ischemic and scarred myocardium. Both ischemic and scarred myocardium will usually be observed as defects in the immediate postexercise scan. Ischemic defects fill in over time, whereas defects from scarring persist. Wall motion can be reduced secondary to reversible ischemia as well as scar. Thus, areas that demonstrate delayed thallium uptake are believed to be consistent with reversible ischemia, and when such areas correspond to bypassable coronary arterial lesions as determined from coronary cineangiography, a beneficial effect on segmental wall function from bypass surgery might be anticipated. Obviously when mechanical lesions such as mitral insufficiency, ventricular aneurysm and ventricular septal defect are combined

TABLE I
Preoperative and Postoperative Measurements of Ventricular Function

Variables of Ventricular Function	Case 1		Case 2	
	Preop	Postop	Preop	Postop
NYHA class[33]	IV	II	IV	II
PCW or LVEDP (mm Hg)	36	11	35	14
Cardiac index (liters/min per m^2)	1.6	2.4	1.7	2.5
Cardiothoracic ratio	0.56	0.52	0.56	0.49
Ejection fraction (%)*	15	27	12–15	33
Exercise tolerance test†				
Duration (min)	1.7	3.0	6.6	9.7
Reason for stopping	Dyspnea	Claudication	Dyspnea	Fatigue
Heart rate (beats/min)	95 → 120	80 → 107	108 → 150	76 → 188
Blood pressure (mm Hg)	130/80 → 140/80	150/70 → 190/80	105/80 → 110/80	110/70 → 130/70
ECG changes	S-T depression	None	None	None
Thallium stress test				
Ischemia	Septal, inferoapical	None	Septal, anterior	None
Scar	None	None	Large inferior	Small inferior
Lung uptake	Increased	None	Increased	Diminished

* Preoperative obtained from ventriculogram; postoperative obtained from gated blood pool scan. † Bruce protocol.
ECG = electrocardiogram; LVEDP = left ventricular end-diastolic pressure; NYHA = New York Heart Association; PCW = pulmonary capillary wedge pressure; Postop = postoperative; Preop = preoperative.

with areas of reversible ischemia and operable coronary artery disease, their simultaneous correction is likely to have an even greater potential for relieving congestive heart failure. Accordingly, the presence of left ventricular failure associated with coronary artery disease does not necessarily preclude a treatable situation. In the presence of reversible ischemia predicted on the basis of the thallium study, segmental asynergy would be anticipated to be reversible, and under these circumstances bypass surgery might be effective.

Results of surgery: The presence of two prior painless myocardial infarctions in the first of our patients made us wonder if he might have exercise-induced ischemia without pain that was contributing to his left ventricular failure. His good surgical result seems to have justified that assumption. In the second patient the postoperative improvement in left ventricular function can be explained at least in part by the correction of mitral regurgitation and removal of left ventricular scar. However, the considerable improvement in findings on postoperative thallium myocardial imaging leads us to believe that correction of silent myocardial ischemia might have played at least a partial role in his improved postoperative condition.

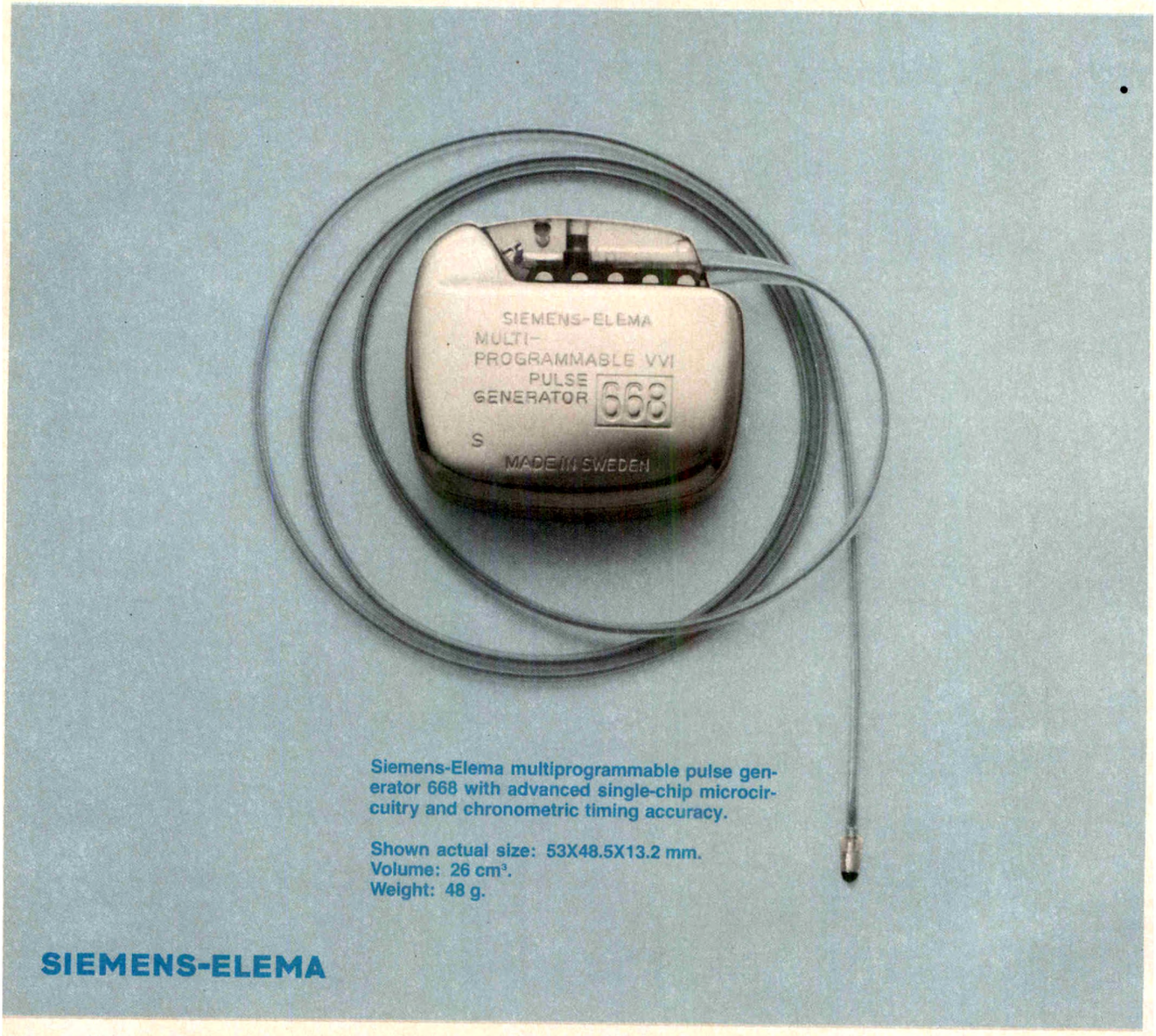
Multiple procedures have been used to evaluate the ability of myocardial revascularization to improve ventricular function. Various investigators[24–29] have documented hemodynamic improvements after revascularization, as well as improved response to atrial pacing,[30] changes in myocardial metabolism,[31] and improvements in myocardial perfusion or left ventricular function, or both, as measured by radionuclide scanning.[32] In addition to the marked subjective clinical improvement in both patients, there was objective evidence (Table I) of improvement in left ventricular function as shown by postoperative hemodynamic measurements, cardiothoracic ratio, ejection fraction and exercise tolerance, and improvement in myocardial perfusion as shown by myocardial imaging. This improvement was anticipated preoperatively by the presence of reversible ischemia with thallium-201 imaging.

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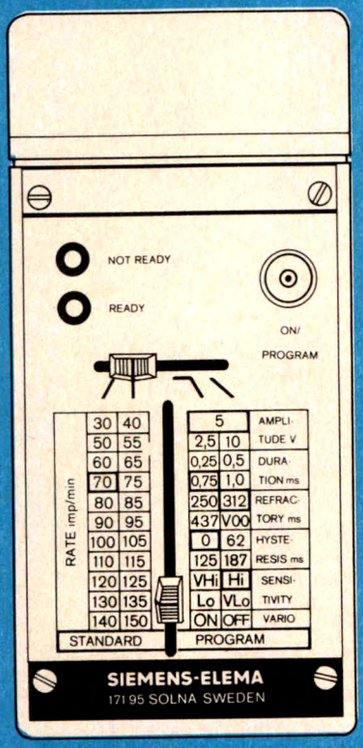
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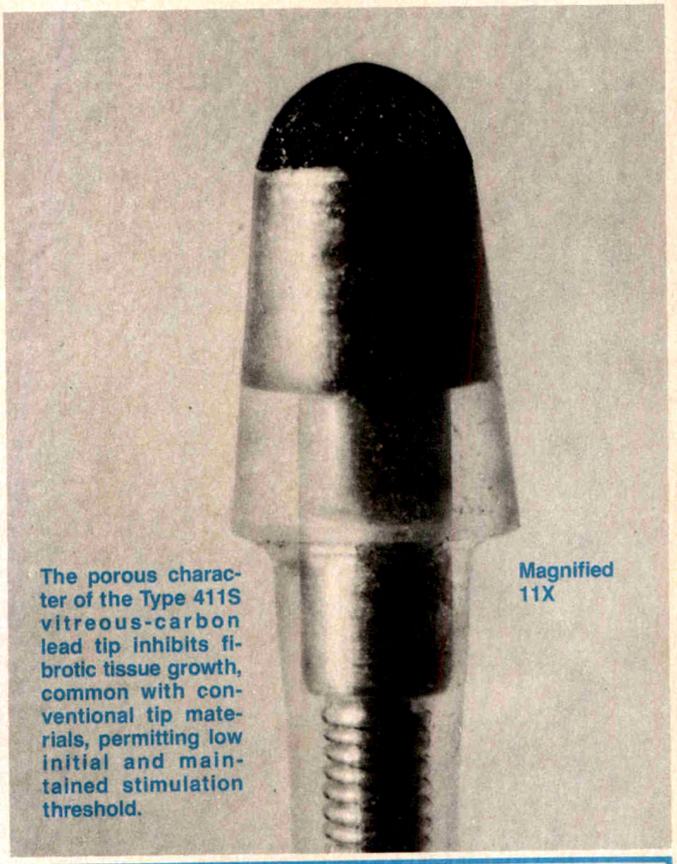
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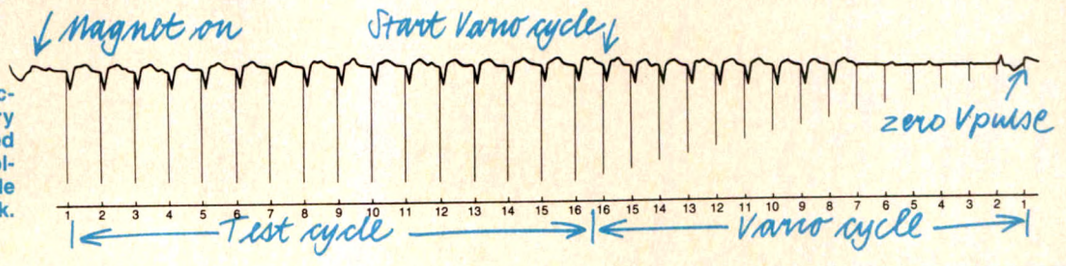


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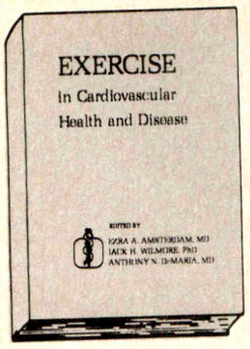
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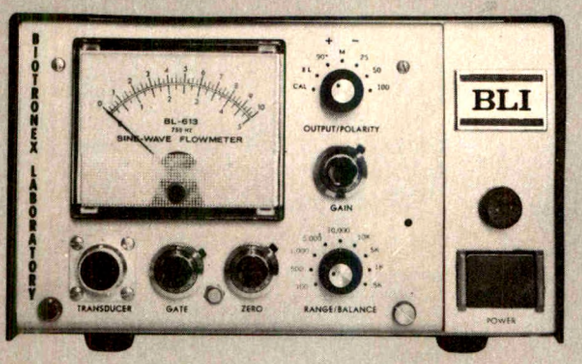
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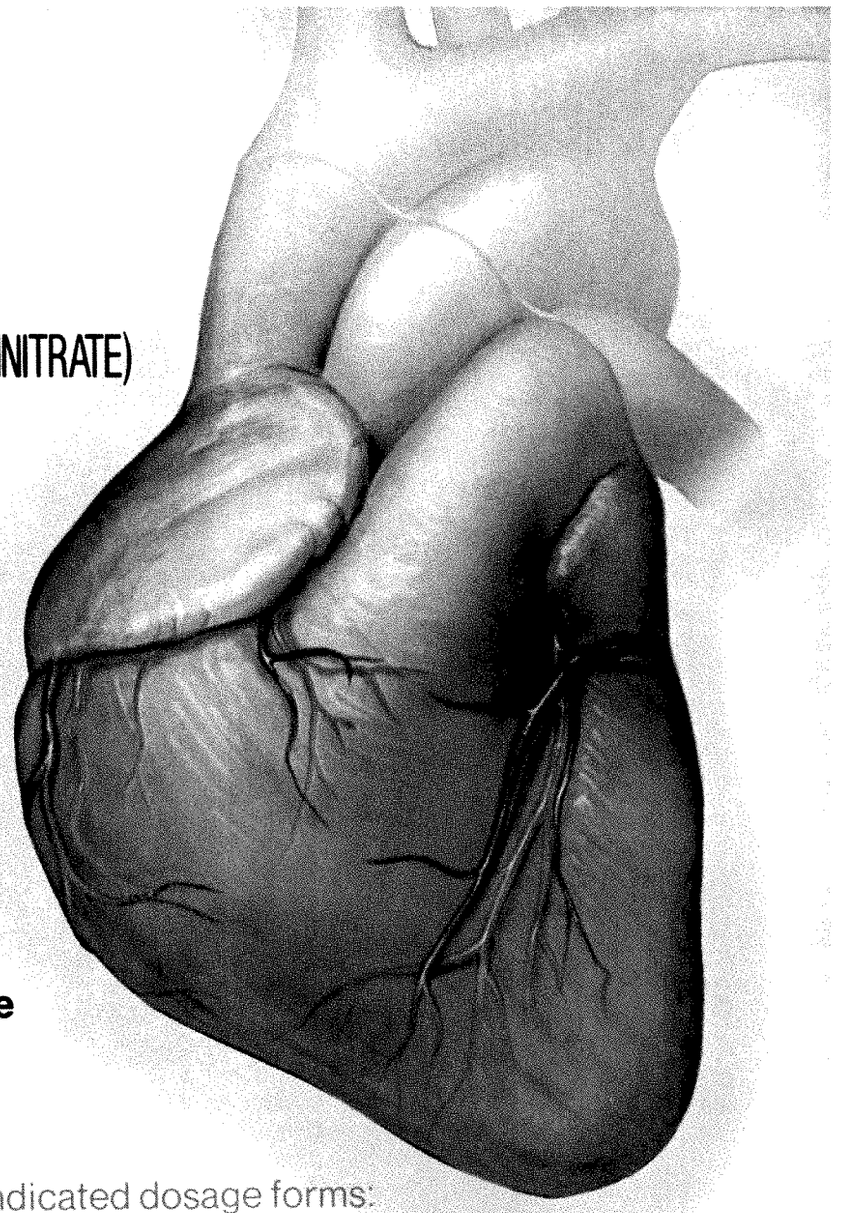


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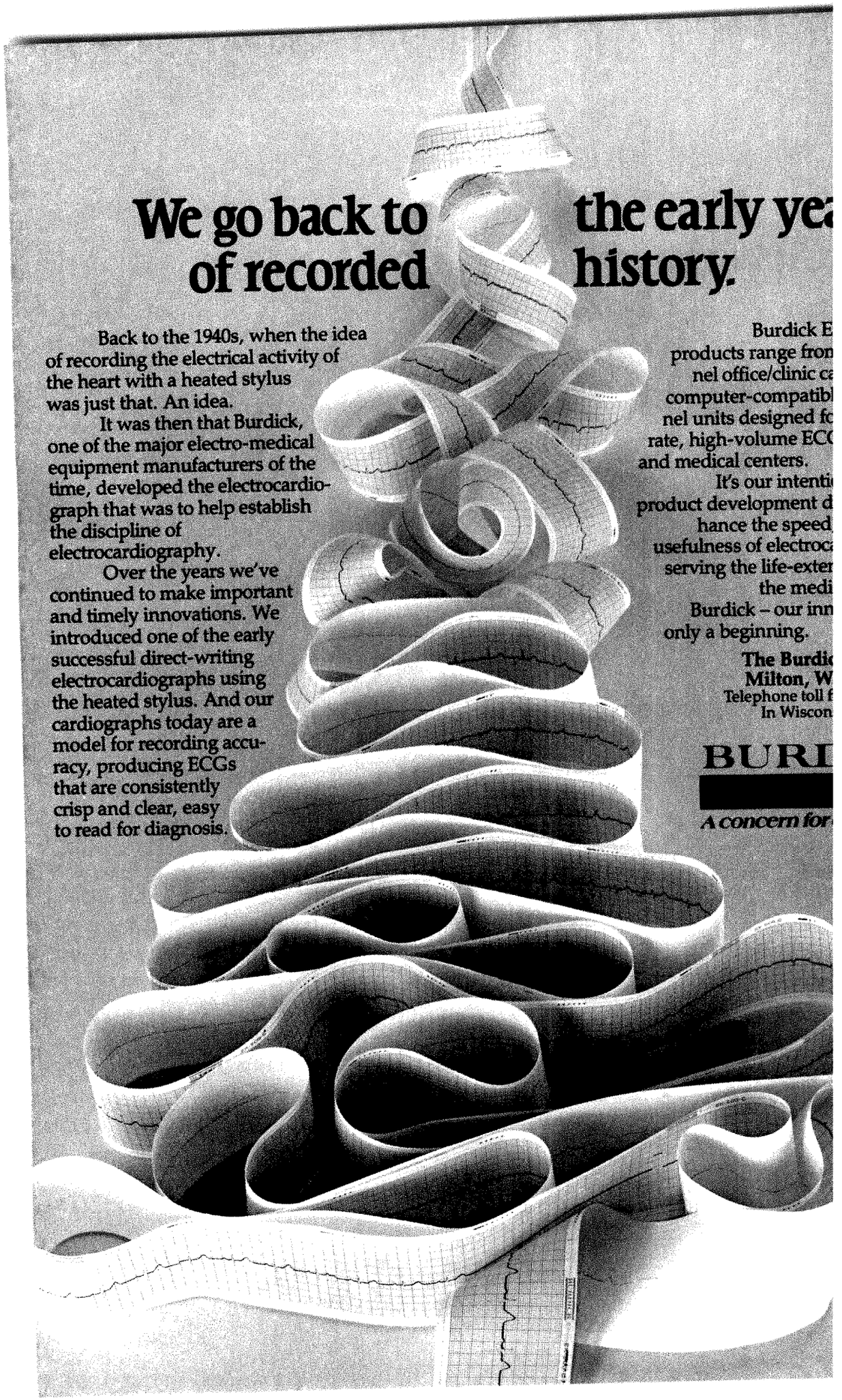
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LETTERS TO THE EDITOR

VARIANT ANGINA PECTORIS AND SYMPATHETIC NERVOUS SYSTEM FUNCTION

obertson et al.[1] found no generalized increase in sympathetic utflow associated with the initiation of attacks of variant ngina and claimed that "germane to this discussion is the ffect of autotransplantation. This procedure has been investigated in the treatment of variant angina with one subject xperiencing relief of symptoms; nevertheless, the patient had ersistence of vasospasm in spite of the interruption of autonomic fibers to the coronary artery. . . . It may mean that he key to coronary vasoconstriction lies in local pathophysiology at the level of the vessel itself independent of central ympathetic outflow." I disagree with this interpretation for he following reasons: (1) The patient of Clark et al.[2] who had oral spasm of the right coronary artery responsible for severe ttacks had no recurrent attacks after autotransplantation. The patient was restudied after operation and spasm was gain demonstrated by the ergotrate stimulation test. The pasm observed after operation was provoked and not spontaneous. The woman has continued to do well 3 years after peration. (2) Recently Cipriano et al.[3] demonstrated that rgonovine maleate induced the same degree of coronary arterial narrowing in heart transplant recipients and in patients vith normally innervated hearts who did not manifest coronary spasm. Thus the normal pharmacologic response to ergonovine maleate was probably due to a direct vasoconstricting action of the drug and this action was independent f extrinsic neural control. (3) In our institution we performed utotransplantation in a man with severe variant angina. Before operation, the coronary arteriogram was normal and pasm of the left circumflex coronary artery was provoked by rgonovine. All drugs (nitrates, amiodarone, nifedipine, diltiazem) failed to obtain even slight relief of symptoms. In the 5 month follow-up period after cardiac autotransplantation vas performed, we observed the following: (a) The patient xperienced no chest pain (however, this finding is not significant because ischemic episodes can occur without pain and fter autotransplantation the paths of pain have been cut). b) Many continuous electrocardiographic recordings showed no S-T segment changes after operation, although such hanges had previously been observed. This finding suggests hat the ischemic episodes had been abolished. (c) On restudy rgonovine was able to reproduce spasm of the left circumflex oronary artery with electrocardiographic changes but without ain. This observation suggests that the coronary "trigger one" can be stimulated (by ergonovine) but is not spontaneously stimulated by the central nervous system. On the basis of the tests used in the study of Robertson et al. and on the basis of these considerations in relation to cardiac autotransplantation, we believe that it is inexact to deny a role to the central sympathetic nervous system.

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REPLY

The careful follow-up Bertrand is undertaking—including repeated continuous electrocardiographic recordings—is critical to eventual understanding of coronary vasospasm. However, we continue to believe that the bulk of evidence supports the hypothesis that the primary abnormality in variant angina lies in the local vasculature rather than in the central nervous system.

Bertrand's patient, like that of Clark et al. (Bertrand's Ref 2), had excessive coronary arterial reactivity to ergonovine maleate both before and after effective autonomic denervation of the heart. Because denervation in itself does not cause excessive reactivity (Bertrand's Ref 3), it would appear that an abnormality independent of innervation exists.

It seems likely that in the presence of the primary vascular abnormality, diverse stimuli could lead to spasm. Ergonovine maleate is the best studied such stimulus, but we would not be surprised if circulating angiotensin, thromboxane A_2, vasopressin or the patient's own sympathetic nervous system might, under appropriate conditions, also serve as stimuli. It is important to recognize that such responsiveness need not imply abnormal levels of angiotensin, thromboxane A_2, vasopressin or adrenergic outflow.

The symptomatic relief achieved by autotransplantation thus far is heartening. The patient of Clark et al. is now doing well 5 years after surgery (Angell WW, personal communication), and Bertrand's patient has had no evidence of spontaneous coronary spasm detectable on electrocardiography. However, the cyclical nature of variant angina is such that remissions of years may occur[1] and optimism concerning this mode of therapy has to be tempered with caution.

Trials of inhibitors of potential stimuli such as angiotensin, thromboxane A_2 and norepinephrine will further our knowledge concerning the specificity of the vascular abnormality. Surgical interventions such as those of Bertrand are also pivotal in unraveling the mystery of this disease.

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PLASMA PROPRANOLOL LEVELS IN ANGINA PECTORIS

Can the antianginal effects of propranolol be judged from its plasma concentrations? The duration of action of beta adrenergic receptor blockade has been disputed.[1–11] Previous investigators[1–5] have shown a dissociation between the rate of clearance of propranolol from blood and the slower disappearance of its effects. Thus, the longer duration of the action

of propranolol is somewhat puzzling, given its short elimination half-life.[12]

Whereas some investigators[6] believe that the hemodynamic duration of action correlates closely with serum levels of the drug, others[1-5] believe that the hemodynamic effects last considerably longer than the serum levels would indicate. Thadani and Parker[13] recently reported that, despite the short mean half-life of propranolol of 3.98 hours after the 80 mg dose and 4.28 hours after the 160 mg dose, the improvement in exercise tolerance and other circulatory effects persisted for 12 hours. They suggested that administration of propranolol twice daily should be adequate in treating patients with stable angina pectoris and concluded that routine measurement of plasma propranolol level is of little practical value in the management of such patients. I agree with their former suggestion but cannot agree with their latter conclusion for the following reasons:

According to a method proposed by Levy,[14] one can translate the pharmacokinetics of a drug to the pharmacodynamics. The effect (E) versus time data in the postabsorptive phase can be described by the equation[14]:

$$E = E_0 - \frac{m \cdot K_{el}}{2.3} \cdot t, \qquad (1)$$

where E_0 is the extrapolated zero time intercept and m is the slope of a plot of effect versus log plasma concentration (log C). This plot of concentration-effect relation is generally linear over the range of 20 to 80 percent of the maximal effect and can be represented by the equation[14]:

$$E = m \cdot \log C + r, \qquad (2)$$

where r is a constant.

When I use the average data of time course of plasma propranolol concentration (ng/ml) given in Table I of Thadani and Parker[13] and the corresponding data on percent increase in treadmill walking time to the onset of angina (P_1) after each dose of propranolol as one of the pharmacologic effects they examined during their experimental period (their Table II),[13] the average effect-concentration (log C) data were obtained as shown in my Figure 1. This relation was fit to a straight line ($E = 34.53 \cdot \log C - 9.96$, $r = 0.93$, $p < 0.001$) according to the equation (2) by linear regression analysis, where the value of the slope (m) was 34.53.

The mean elimination half-life ($t_{1/2}$) of 4.28 hours after the 160 mg dose[13] yields the elimination rate constant (K_{el}) of 0.162 hour^{-1}, which indicates that the disappearance rate of propranolol from the plasma as percent reduction per unit of time is 16.2 percent/h.

In contrast, when I use the observed data on percent increase in treadmill walking time to the onset of angina (P_1) after the 160 mg dose with time (as illustrated in their Fig. 2)[13] and calculate the correlation of the pharmacologic effect (P_1) with time from the linear decline 2 to 24 hours after oral drug administration, the following relation is obtained:

$$E = 65.08 - 2.41 \cdot t, \qquad (3)$$

where the value of 65.08 is the initial effect extrapolated from the linear decay of the effect with time at the zero order rate, and the value of 2.41 is the slope indicating the declining rate of drug effect in this case. When one estimates the declining rate of drug effect from this relation as percent reduction/h, the value of 3.7 percent reduction/h can be obtained. The effect declines linearly with time or at the zero order rate, even though drug level from the plasma falls exponentially or at the

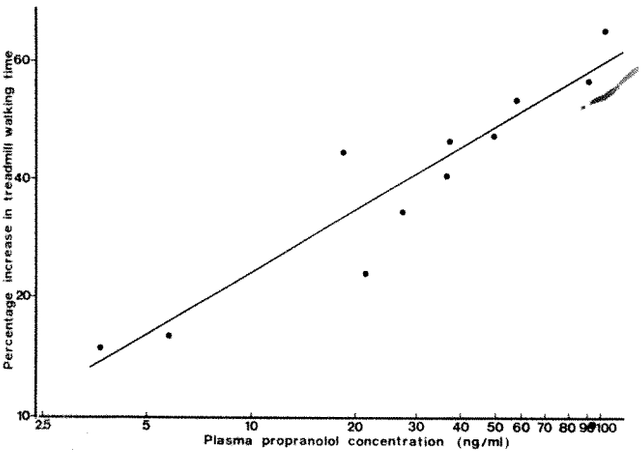


FIGURE 1. Relation between plasma propranolol concentration and percent increase in treadmill walking time to the onset of angina. The group mean values of plasma propranolol concentration (C) were obtained from Table I of Thadani and Parker.[13] The corresponding data of percent increase in treadmill walking time to the onset of angina (E) were calculated from the group mean values given in their Table II. The best fit of the solid line was: $E = 34.53 \cdot \log C - 9.96$ ($r = 0.93$, $p < 0.001$).

first order rate, and the duration of action of the drug is much longer (approximately 4.4 times) than the pharmacokinetic elimination half-life of propranolol. Furthermore, if one substitutes the values of m (34.53) and K_{el} (0.162 hour^{-1}) for $-m \cdot K_{el}/2.3$ in the equation (1), $E = E_0 - 2.43 \cdot t$ can be derived. The value of 2.43 generated from a theory of Levy[14] translating the kinetic data to the pharmacologic effect is very close to the actually observed value of 2.41. Thus, either as observed or as theoretically calculated, the 12 hour duration of action of propranolol observed by Thadani and Parker[13] is explainable by the shorter half-life of 4.28 hours after the 160 mg dose. Although I am analyzing all their data on circulatory effects (their Table II) in relation to plasma propranolol concentration (their Table I), it can be stated at present that the majority of their hemodynamic data can be predicted from the plasma propranolol concentration.

We recently observed that when we measured the beta blocking activity of timolol using maximal exercise tachycardia as a given response, the effects declined linearly with time, even though plasma levels fell exponentially, and thus demonstrated that the pharmacokinetic elimination half-life was much shorter than the drug's duration of action in normal human volunteers.[15] According to Perrier and Gibaldi,[9] it has been suggested on theoretical grounds that propranolol's action is related to a tissue level that equilibrates only slowly with the plasma level. However, our results[15] were in agreement with McDevitt and Shand,[10] who observed that the beta adrenergic blocking effect of intravenously administered propranolol was at all times a predictable function of its plasma concentration. In our dog experiments[16] with another beta blocking agent, sotalol, it was more clearly shown that pharmacokinetic data can be translated into pharmacologic effects by applying a theory developed by Levy.[14] The relation expressed in the equation (1) has interesting implications. It indicates that, despite a direct relation between drug concentration in plasma and intensity of the elicited pharmacologic effect, the rates of decline of these two quantities can follow different kinetics and, therefore, not be parallel. Furthermore, there was good agreement between such translated findings as the rate of decline of drug effect ($-m \cdot K_{el}/2.3$)

sing the slope of the log concentration-effect relation (m alue) and the first order rate of elimination rate constant K_{el}) and with findings actually observed in the time-action ourse of beta blockade as discussed earlier. Mayersohn and 'errier[17] recently proved that cocaine plasma concentration esponse time data analyzed by a pharmacokinetic model are n reasonable agreement with their application of Levy's heory[14] to actual published data.[18,19] This analysis is further upport for Levy's theory,[14] and our observations[15,16] strongly uggest that the significance of the kinetic disposition of a drug ıust be evaluated in relation to its pharmacologic effect and ime. However, because not only K_{el} but also m can vary to a ertain extent in a series of similar pharmacologic agents as bserved among different persons, there is a possibility of ıodifying the relation between the time course of the body rug content and the time-intensity course of a pharmacologic ffect.

Much discussion has focused on the possible therapeutic alue of the various ancillary pharmacologic properties of the eta receptor antagonists. However, Thadani and co-workrs[20,21] clearly demonstrated in their well controlled clinical rials using various beta receptor antagonists in patients with xercise-induced angina pectoris that these drugs with different pharmacologic properties were equally efficient in mproving exercise tolerance at their equipotent dose prolucing beta blockade effect. This indicates that the ancillary harmacologic properties are of little or no direct relevance n the relief of anginal pain but the beta blockade effect itself s of the most importance. Although their studies cannot upply a direct answer as to the specific importance of the nchanged agent or its metabolites[22,23] in the relief of angina, heir observation that similar symptomatic and electrocarliographic effects result after intravenous and oral adminisration in all instances implies some evidence that such meabolites are probably of therapeutic relevance only insofar s the drugs exert antagonistic action against endogenous ympathetic activity at the cardiac beta receptor sites.[20] Therefore, I assume that the beta receptor blockade itself is elated to the antianginal effect, which implies that the plasma evels of beta adrenoreceptor blocking agents should be apropriately interpreted. It is highly probable that the obserations of previous investigators[1–11] studying the relation etween plasma concentrations of beta blockers and the harmacologic effects are correct as experimental results but nay be incorrectly interpreted because they have not applied he appropriate principle for translating pharmacokinetics o pharmacodynamics of a drug.[14]

Finally, the relations between the logarithm of plasma oncentration and effect and effect and time must be taken nto account in order to interpret adequately the usefulness f determining the plasma level of the drug. It is evident that urther studies are required for such critical points before the lasma concentration of beta blocking drugs can become a herapeutic guide.

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REPLY

Ishizaki has used our average data to examine the effect-concentration relation and found that the relation between the average percent increase in treadmill walking time to angina and the log plasma concentration fit to a straight line. Utilizing the theory proposed by Levy, translating the kinetic data to the pharmacologic effect, he has been able to explain the 12 hour duration of action of propranolol with its shorter elimination half-life of 4.28 hours after the 160 mg dose. We agree with his reasoning and conclusion that there was indeed a good effect-concentration correlation when one examines the average data. This was the case when we examined the relation between treadmill walking time to angina and plasma propranolol concentration. However, we would caution against utilizing the average plasma propranolol concentration in predicting a response in a given person because of the marked interindividual variations in plasma propranolol concentrations after a given dose reported by us and other workers. For this reason we correlated the effect-concentration relation in individual patients (our Fig. 4) and found a marked interindividual variation in effect-concentration relation. Furthermore, in many of the individual patients, increases in treadmill walking time to angina were similar when the plasma concentrations were above 50 ng/ml or below the level of detection by the analytic method employed. In view of these observations, we still believe that routine measurement of plasma

propranolol levels is of little value in the routine management of patients with angina pectoris.

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HEART RATE RESPONSE TO ORAL PRAZOSIN IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

Packer et al.[1] indicated a significant negative chronotropic action of prazosin in nine patients with severe chronic congestive heart failure. We recently evaluated the hemodynamic effects of 3 to 10 mg of oral prazosin in 15 patients with severe congestive heart failure. Although, at peak effect the change in cardiac index, left ventricular filling pressure and systemic vascular resistance in our patients was comparable with that found by Packer et al., the response of heart rate and systemic arterial pressure differed significantly. The decrease of mean blood pressure in our group after the administration of prazosin was significant but of lesser magnitude (-6.2 ± 2 mm Hg versus -18.3 ± 2.5 mm Hg). In contrast to the significant decrease in heart rate (from 84 ± 3 to 77 ± 4 beats/min, $p < 0.01$) found by Packer et al., the mean heart rate in our patients increased slightly (from 86 ± 4 to 89 ± 4), but the change did not reach statistical significance. Individual analysis of our data demonstrated a decrease of heart rate in only three patients, no change in four and an increase in eight patients. Because the mean dose of prazosin in our group was 6.6 mg compared with 5 mg administered by Packer et al. and seven of our patients received 5 mg or more, the described negative chronotropic effect of prazosin can not be interpreted as dose-related.

Mehta et al.[2] administered 4 mg of oral prazosin to 10 patients with congestive heart failure and showed a reduction of mean arterial blood pressure from 92 ± 5 to 78 ± 4 mm Hg ($p < 0.01$) but no significant change in heart rate. Miller et al.[3] described a tendency of the heart rate to decline after 2 to 7 mg of oral prazosin in 10 patients with congestive heart failure; however, this finding was not statistically significant. Whereas in hypertensive patients the negative chronotropic effect of prazosin is dissimilar to the tachycardiac effect of hydralazine, comparative evaluations of the hemodynamic effects of both drugs in the same normotensive patients with congestive heart failure showed no significant difference in heart rate response[4,5] We believe therefore that the overall information published to date does not allow the conclusion that prazosin exerts a direct negative chronotropic effect in patients with severe congestive heart failure.

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REPLY

Not all studies on the hemodynamic effects of prazosin in patients with heart failure have described a decrease in heart rate during therapy. However, we are not alone in our observation; other investigators[1,2] have observed this type of response. Although Elkayam et al.[3] did not observe such an effect in their study, one major difference between their study and ours is that, although the average dose they evaluated was large (6.6 mg), this was not the first dose of the drug administered, as it was in our study; rather, all patients received 3 mg initially and were sequentially given larger doses until some patients received 10 mg. As with the other hemodynamic effects of prazosin, rapid tolerance to the negative chronotropic effects may develop with repeated administration of the drug.[4]

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PROPRANOLOL AND ARRHYTHMIA IN HYPERTROPHIC CARDIOMYOPATHY

McKenna et al.[1] inferred that our statement[2] that "a daily dose of propranolol of less than 320 mg was rarely effective" was related to suppression of ventricular arrhythmias by beta blockade. They also implied that our use of large doses of propranolol was effective in suppressing complex ventricular arrhythmias. Our report emphasized the fact that daily doses of propranolol of more than 320 mg/day (average 462 mg/day) were necessary to achieve *"complete" beta blockade and symptomatic improvement* in most of our patients with hypertrophic cardiomyopathy. We did not state that propranolol was used primarily for elimination of arrhythmias. Propranolol doses greater than 320 mg/day were titrated by the symptomatic status of the patient. We suspected that *improved diastolic compliance* after propranolol therapy was responsible for the lessening of signs of congestive heart failure and dyspnea in our patients. Lessening of palpitations, presyncope and syncope appeared to have been related to arrhythmia control. However, antiarrhythmic agents *in addition to* propranolol were necessary in the great majority of our patients. Although we also had patients with arrhythmias, including short runs of ventricular tachycardia in the absence of symptoms, as well as patients with symptoms in the absence

of rhythm disturbances during ambulatory monitoring, the relation between suppression of potentially life-threatening arrhythmias and symptomatic improvement was striking. Potentially life-threatening arrhythmias were suppressed in all but one patient who had residual rare couplets only; palpitations and presyncope lessened in most; syncope was eliminated in all, and there have been no deaths.[3]

Regarding the antiarrhythmic properties of propranolol, our manuscript clearly indicates that potentially life-threatening arrhythmias were controlled with propranolol in only 4 of 11 patients; the addition of other antiarrhythmic drugs was necessary in the remainder.[2] This was also the case in our larger group (33 patients).[3,4] We found that control of 77 percent of complex forms of arrhythmia required other antiarrhythmic drugs in addition to propranolol. However, in 21 percent frequent premature ventricular complexes (grade 2 of Lown's classification[5]) *without complex forms* decreased in frequency to grade 1 or 0 with propranolol alone. Woosley and his associates[6] recently reported on the use of propranolol as an antiarrhythmic drug. They found that ventricular arrhythmias including ventricular tachycardia responded in one third of 32 patients at doses of 160 (or less) mg/day, but an additional 40 percent responded at doses of 200 to 640 mg/day. They also found that some patients with partial or complete suppression of ventricular arrhythmias at a given dose of propranolol had an increase in arrhythmia severity when the dose was increased. Therefore, it is not surprising that some of the patients of McKenna et al. had arrhythmias even on a regimen of 800 mg/day of propranolol, since larger doses do not invariably produce better results. It appears that control of malignant ventricular arrhythmias requires more than one antiarrhythmic agent in the great majority of cases, as also reported by Lown et al.[5]

We postulate that beta blocking doses of propranolol should be used in *all symptomatic patients* with hypertrophic cardiomyopathy because of this drug's value in controlling symptoms, presumably by improving diastolic compliance. In addition, we believe that our routine use of propranolol may have prevented the onset of atrial fibrillation[3] and *contributed* to the control of ventricular arrhythmias when used with other antiarrhythmic agents.

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REPLY

We appreciate that Frank et al. used propranolol primarily for its hemodynamic and symptomatic benefits; this is clearly stated in their paper. Their comments on the possible benefits of propranolol related to arrhythmia control are somewhat ambiguous, however. We quote: "Because there have been no fatalities in our 22 protocol patients . . . we suspect that high doses of propranolol alone may have been responsible for controlling life-threatening arrhythmias." And: "In contrast to our experience Ingham et al. reported that propranolol was not effective as an antiarrhythmic agent in patients with . . ." We entirely agree with the conclusion of Frank et al. that beta blocking doses of propranolol should be used in symptomatic patients for relief of symptoms, but we have no evidence in our patients that propranolol prevented the onset of atrial fibrillation. Propranolol may indeed help to control arrhythmias when given with other antiarrhythmic agents, but we do not have the proof.

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MYOCARDIAL BRIDGING AND IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

Several workers[1,2] have recently reported septal perforator compression, especially in idiopathic hypertrophic subaortic stenosis. We noticed septal perforator compression 1 year ago in a patient who had idiopathic hypertrophic subaortic stenosis and myocardial bridging of the left anterior descending coronary artery. Since then, a coronary arteriogram was obtained systematically in the 12 patients in the department who were hospitalized for idiopathic hypertrophic subaortic stenosis. From 1974 to 1978, seven other arteriograms had been performed in cases of idiopathic hypertrophic subaortic stenosis. We compared the results of these 19 arteriograms with those of 16 patients with aortic stenosis: All patients with idiopathic hypertrophic subaortic stenosis had a significant (30 mm Hg or greater) intraventricular pressure gradient at rest or on provocation with isoproterenol or premature ventricular depolarization (average 79 mm Hg). Eighteen patients had a characteristic left ventricular angiographic pattern together with typical phonocardiographic and carotid pulse curves. An echocardiogram obtained in 16 of these cases was diagnostic of idiopathic hypertrophic subaortic stenosis in 15.

We found myocardial bridging of the left anterior descending coronary artery in five patients with idiopathic hypertrophic subaortic stenosis (26.3 percent), whereas the frequency of myocardial bridges in large series of coronary arteriographic studies is estimated to be between 0.1 and 0.7 percent. We found no myocardial bridge in any of the 16 patients with aortic stenosis.

Unlike Pichard and Kostis and their co-workers, we did not find systolic compression of the septal perforator arteries in all, but in 12 cases of idiopathic hypertrophic subaortic stenosis (63.2 percent). Like Pichard,[3] we noticed septal perforator compression in only one case of aortic stenosis (5 percent in our series). The reasons for the discrepancy on this point between the results of Pichard and our group and those of Kostis are not obvious.

We found no statistically significant correlation between the degree of septal perforator compression and either the hemodynamic (especially the intraventricular pressure gradient) and echocardiographic features or the presence of angina in patients with idiopathic hypertrophic subaortic stenosis.

The role of myocardial bridging in myocardial ischemia was

l demonstrated by Noble et al.[4] Finding it in a case of idathic hypertrophic subaortic stenosis, especially in assotion with a severe septal perforator compression, is for us rther argument for carrying out an effective beta adrenic blocking regimen. Therefore, coronary arteriography uld be an indispensable step in any complete investigation diopathic hypertrophic subaortic stenosis.

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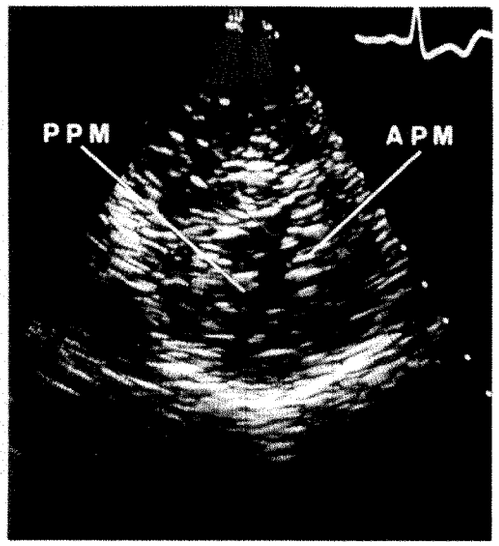
ECHOCARDIOGRAM IN APICAL HYPERTROPHIC CARDIOMYOPATHY

:he article by Hiroshi Yamaguchi et al.,[1] it is questionable he arrow in Figure 9 is depicting the border of the left ıtricular posterior wall or the echoes of the papillary scle.

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amaguchi H, Ishimura T, Nishiyama S, et al. Hypertrophic nonobstructive cardiomyoathy with giant T waves (apical hypertrophy): ventriculographic and echocardiographic ıatures in 30 patients. Am J Cardiol 1979;44:401–12.



IRE 1. Apical hypertrophic cardiomyopathy. End-diastolic frame from a two dimensional ıcardiogram at the level of the papillary muscles (short-axis view). The thickness of the septum and the posterior free wall is markedly increased. The papillary muscles ılso hypertrophied. Obliteration of the apical cavity is clearly demonstrated. APM = ·olateral papillary muscle; PPM = posteromedial papillary muscle.

REPLY

The source of the multiple echoes in the M mode echocardiogram of the left ventricle has generally been thought to be the papillary muscles.[1] In the cases of apical hypertrophic cardiomyopathy we presented, the posterior wall thickness may include some parts of the papillary muscles. The obliteration in the apical cavity is therefore composed of the hypertrophied papillary muscles muscles as well as the hypertrophied septum and posterior wall (Fig. 1).[2–5]

Two dimensional echocardiography also suggests that hypertrophied papillary muscles are related to the apical obliteration. However, M mode echocardiography sometimes makes it difficult to obtain and record the maximal internal dimension of the left ventricle during the scanning and may artificially produce a false apical obliteration even in normal subjects. It is therefore necessary to use two dimensional echocardiography as well as simultaneous M mode echocar-

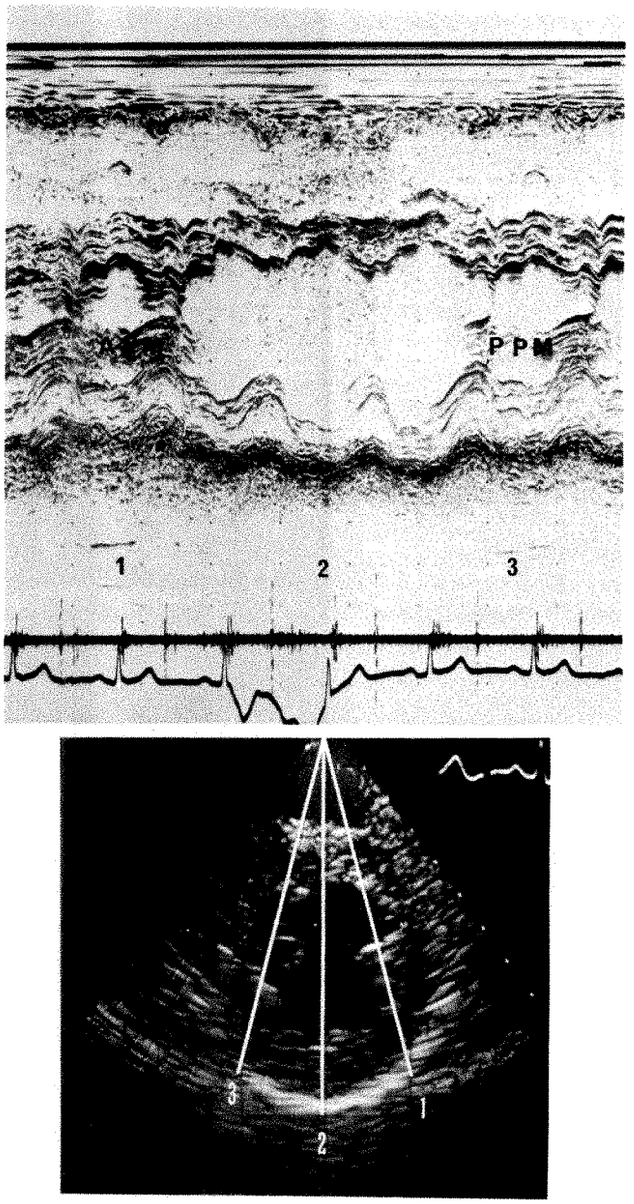


FIGURE 2. M mode (**top**) and two dimensional (**bottom**) echocardiogram simultaneously recorded in a normal subject. The echoes of the papillary muscles appear to produce a false cavity obliteration in the apical segment.

diography for evaluation of hypertrophic cardiomyopathy (Fig. 2). We believe that cineangiographic confirmation of ventricular morphology is even more important in obtaining a definite diagnosis of apical hypertrophic cardiomyopathy. The cineangiogram can clarify the hypertrophic pattern of the apical segment as well as the presence or absence of coronary artery disease.

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FORMAL CARDIAC REHABILITATION

I am concerned that the article by DeBusk et al.[1] may give the impression that a formal cardiac rehabilitation program may be without benefit for many patients recovering from an acute myocardial infarction. Follow-up data collected from patients recovering from an acute myocardial infarction who were hospitalized at Cedars-Sinai Medical Center, Los Angeles and who did not enter a formal cardiac rehabilitation program showed the following:

1. The percent of patients who engaged in unrestricted physical activities before and after acute infarction was 54 and 11 percent, respectively.

2. The percent of patients who engaged in moderate activity (walking 1 or more miles daily, and maintaining unrestricted social and occupational activities) before and after acute infarction was 21 and 33 percent, respectively.

3. The percent of patients who were sedentary (performing only routine household chores and engaging in no unusual physical activities) before and after acute infarction was 13 and 35 percent, respectively.

4. The percent of patients who were restricted (not able to perform routine household activities) before and after acute infarction was 6 and 16 percent, respectively.

5. Overall, 6 percent of patients increased their activity level after an acute infarction, 41 percent showed no change and 53 percent decreased their activity.

Thus, among our patients who did not undergo formal cardiac rehabilitation, over one half became either sedentary or restricted in activity. With formal rehabilitation, only 11 percent of patients were in these activity classifications. To base conclusions on a study in which the average "no training" patient was walking an average of 3 miles/day may not be valid, because in our experience 51 percent of postinfarction patients become either sedentary or restricted in activity. Formal cardiac rehabilitation programs have many benefits. Not least among them is that they motivate postinfarction patients who would otherwise become sedentary or restricted in activity to a greater level of physical exertion under close supervision from which, presumably, flow the benefits, including a longer life for the average patient in such a program.[2] The low level home exercise programs suggested by De Busk and colleagues as an alternative to formal cardiac rehabilitation appear to be suitable for only a small minority of such patients, since 94 percent of patients without formal training show either no change or decreased activity after acute infarction.

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REPLY

Most patients probably are less physically active after myocardial infarction, and Vyden properly points out that our "no training group" was not truly a control group in the sense that patients underwent an intervention—treadmill exercise testing—as a prerequisite for entry into the study. Indeed, such patients reported walking considerable distances each day. And this is one of the major points we wished to make: Performance of the treadmill test in itself appears to increase patients' confidence in their capacity to perform physical activity and they become more active than they would have been without the test. Is this not "formal rehabilitation"? If it is safe for selected patients to walk 3 miles/day and if there are potential psychological and physical benefits to be had from this cost-free, readily available activity, how "formal" does rehabilitation need to be?

The primary objective of our study was to establish whether a relatively low level, short-term exercise training program, commencing soon after the acute event, would significantly augment the substantial increase in functional capacity that occurs spontaneously after clinically uncomplicated myocardial infarction. The increase in functional capacity was found to be greater in patients without ischemia who underwent exercise training in a supervised gymnasium program than in similar patients who received no formal training. Similarly, patients without ischemia who underwent home exercise training attained a higher absolute functional capacity at 11 weeks than similar patients who received no formal training. These differences, although *statistically* significant, may have marginal *clinical* significance, because all patient groups attained an average functional capacity of at least 9 METs by the 11th week after infarction. A functional capacity of 8 METs is considered an *"exit criterion"* for cardiac exercise training programs.[1] Such patients would be capable of performing most vocational and avocational activities.[2]

Our study thus demonstrates physiologic benefits for *both* gymnasium and home exercise training programs commencing soon after clinically uncomplicated myocardial infarction. Our study addressed only the short-term effects of exercise training on cardiovascular performance, not the impact of training on psychological status or prognosis. No one should conclude from our study that formal rehabilitation programs are without benefit.

Yet it is clear that rehabilitation programs as presently constituted can accommodate only a small minority of postinfarction patients. A rough estimate of the gap between the demand for and the supply of such programs is as follows: 600,000 persons survive myocardial infarction each year; at least two thirds of them—400,000—are free of major complications and therefore medically eligible to participate in exercise training programs. If one assumes that only persons aged 70 or less participated, 300,000 patients would be avail-

ible to enter medically supervised exercise training programs. Existing programs in the United States accommodate no more than 200,000 patients with coronary disease annually. If the capacity of such programs were increased 50 percent by reducing the duration of participation, the entire capacity of these programs would be absorbed by postinfarction patients, leaving no room for patients with angina pectoris or those who have had coronary bypass operations. The problem does not stop there, because a sizable proportion of postinfarction patients reside in communities that are too small (less than approximately 100,000) to support group training programs. Further, even where programs are available, many patients cannot afford to participate for financial or logistic reasons.

Thus, group programs can meet only part of the need to provide "formal rehabilitation." Other approaches are needed to facilitate the return to normal physical activities after myocardial infarction. It is not surprising that patients become less active after infarction: They and their physicians lack information concerning their safe level of activity. Even a low level of effort, such as walking at a rate of 2 to 3 miles/h (2 to 3 METs), represents an advance over the present circumstance in which many patients are unnecessarily restricted soon after infarction. A treadmill exercise test helps to provide assurance that this level of effort is safe for a given patient. Whether the physiologic benefit of exercise training at a level more intense than walking justifies the risk and the cost of formal programs remains to be established. In summary, we believe it is too early to conclude that only formal group programs of rehabilitation can meet the needs of patients recovering from myocardial infarction.

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EFFECTS OF ANTIHYPERTENSIVE THERAPY ON CARDIOVASCULAR RESPONSE TO EXERCISE

The effect of various antihypertensive drugs on blood pressure control during exercise is an area not quite as neglected as apparent from the article by Lee et al.[1] In our laboratory we have systematically studied the long-term hemodynamic effects at rest and during exercise of the following antihypertensive drugs: hydrochlorothiazide, polythiazide, chlorthalidone, alpha methyldopa, clonidine, prazosin, six different beta blocking agents and labetalol. It is true that blood pressure control during exercise often differs from that during rest, and there are large differences in the hemodynamic mechanisms behind the reduction in blood pressure. A relatively recent review (with 106 references) is found in Reference 2. Many papers on hemodynamic effects include observations during exercise. Exercise studies of more recent antihypertensive agents, such as bunitrolol and labetalol, are found in References 3 and 4.

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REPLY

We were aware of the works referenced by Lund-Johansen. However, only pertinent research works with a similar objective or a design comparable with ours were selected for discussion.

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SYSTOLIC HYPERTENSION IN THE ELDERLY—I

Simon et al.[1] present an interesting study on the difference in mechanisms of systolic hypertension in younger and older patients. Given the different mechanisms, the difference in response to propranolol and nitroprusside in the two groups would certainly be expected. However, I disagree with their conclusion that older patients with isolated systolic hypertension should be treated with vasodilators. It certainly has been well demonstrated that systolic hypertension, especially in the elderly, is correlated inversely with survival,[2] but to my knowledge there are no studies that show that treating systolic hypertension in the absence of diastolic hypertension lessens morbidity and mortality. The major cause of systolic hypertension in older patients appears to be atherosclerotic noncompliant vessels, and treating that problem as such cannot be done. Furthermore, the therapy of systolic hypertension may decrease diastolic pressures to levels lower than desired, resulting in lower perfusion pressures than desired. This, of course, could be particularly deleterious in older patients with coronary artery disease. Older patients are also prone to the development of symptoms of orthostatic hypotension, and antihypertensive medications in older patients with isolated systolic hypertension may exacerbate these symptoms. Therefore, I believe that older patients with systolic but without diastolic hypertension should generally not be treated with antihypertensive medications.

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SYSTOLIC HYPERTENSION IN THE ELDERLY—II

We are especially interested in the suggestion of Simon et al.

that "nitroprusside-like" drugs might prove successful in controlling systolic hypertension in the elderly. However, certain of their findings are puzzling: (1) In the older patients receiving nitroprusside, the total peripheral resistance increased. Although this increase was statistically nonsignificant, it is difficult to interpret in light of the known action of nitroprusside: arteriolar dilatation. (2) The authors refer to the effect of nitroprusside-like drugs on compliance of the aorta without giving examples of such drugs. How do the authors explain the increase in peripheral resistance, and which nitroprusside-like drugs would they recommend for therapy?

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REPLY

The purpose of our study was to determine the mechanisms of systolic hypertension in younger and older patients. Drugs were used to confirm the described mechanisms. Because nitroprusside was given intravenously to our patients, we mentioned the use of vasodilating drugs to treat systolic hypertension in the elderly only as a possibility. However, several recent studies provide indirect evidence supporting the possibility of such treatment.

Epidemiologic studies[1–4] have shown that systolic hypertension, especially in the elderly, is correlated inversely with survival. The Veterans Administration Cooperative Study group,[5] evaluating the influence of age on the effectiveness of antihypertensive treatment, found that in patients more than 60 years of age the rate of morbid events was 62.8 percent in the control group and 28.9 percent in the treated group. Subsequently, the effectiveness of treatment in preventing morbid events (that is, the difference between the incidence rate of major complications in the control and treated groups divided by the incidence rate in the control group) was 54 percent in the patients aged 60 or more years. More recently, the side effects of antihypertensive therapy in patients more than 60 years of age were extensively studied by the European Working Party on High Blood Pressure in the Elderly.[6,7] During a 2 year follow-up period, the antihypertensive treatment had no major deleterious effects in relation to coronary heart disease or orthostatic hypotension. The main disturbance was an increase in serum creatinine and uric acid that was maintained for 2 years. Because the antihypertensive drugs were hydrochlorothiazide, triamterene and methyldopa,[7] the results of the study suggest that new types of treatment for the elderly should be of interest.

Several vasodilating drugs have recently been proposed for use in clinical pharmacology. Most of them have minimal secondary effects on the sympathetic nervous system. If they could increase arterial compliance, their antihypertensive effect in the elderly should be considered. Table I shows, for example, the changes in systolic pressure observed after intravenous nitroglycerin in patients with hypertension.[8] Both in patients with borderline and in patients with sustained hypertension, a significant increase in arterial compliance was observed. In patients with borderline hypertension, this increase was associated with an important baroreflex response, causing an elevation in heart rate, diastolic pressure and total peripheral resistance, as described in detail elsewhere.[8] In patients with sustained hypertension, the increase in compliance was not associated with a significant change in total peripheral resistance. This peculiar effect was due to the use of small doses of nitroglycerin. Similarly, we used small doses of nitroprusside in our study of systolic hypertension. With such doses, it is possible to show the direct effect of vasodilating drugs on large arteries and the resultant predominant decrease in systolic pressure. Of course, with larger doses, arteriolar dilation occurs, causing a decrease in both systolic and diastolic pressures.

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TABLE I
Hemodynamic Changes After Intravenous Nitroglycerin (15 γ/min during 15 minutes)

	Patients With Borderline Hypertension		Patients With Sustained Hypertension	
	Basal Value	After Nitroglycerin	Basal Value	Nitroglycerin
Arterial pressure (mm Hg)				
Systolic	137 ± 3	138 ± 2	174 ± 6	157 ± 5†
Diastolic	74 ± 2	80 ± 2‡	97 ± 2	97 ± 3
Mean	99 ± 2	100 ± 3	124 ± 4	116 ± 4
Heart rate (beats/min)	72 ± 3	77 ± 4†	74 ± 3	77 ± 4
LV ejection time (s)	0.352 ± 0.011	0.335 ± 0.013	0.336 ± 0.008	0.310 ± 0.008
Cardiac index (ml/min per m^2)	4361 ± 260	3965 ± 263*	3400 ± 234	3059 ± 202
Stroke index (ml/m^2)	73 ± 3	52 ± 4‡	46 ± 2	41 ± 1
Stroke index/LV ejection ratio (ml/m^2 per s)	173 ± 10	162 ± 10	137 ± 7	134 ± 7
Total peripheral resistance (dynes·s·cm^{-5}·m^2)	1813 ± 124	2103 ± 156*	3024 ± 156	3103 ± 277
Systemic arterial compliance (ml/mm Hg per m^2)	1.27 ± 0.10	2.27 ± 0.34‡	0.90 ± 0.11	1.65 ± 0.27†

*,†,‡ Probability (p) value 0.05, 0.02, 0.01, respectively, in comparison with the basal value.
All values are expressed as mean value ±1 standard error of the mean. LV = left ventricular.

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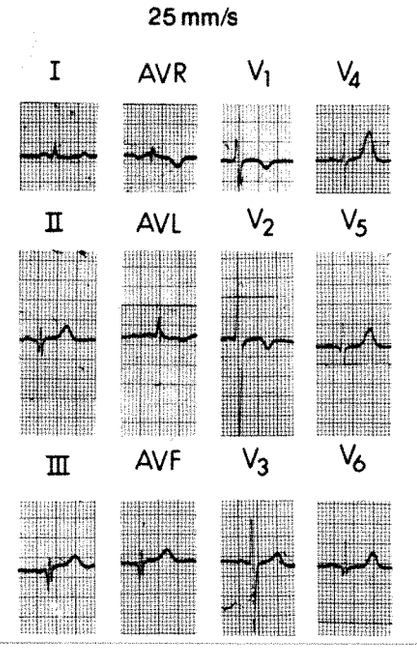
LEFT ANTERIOR FASCICULAR BLOCK AND INFERIOR MYOCARDIAL INFARCTION

The results of Fisher et al.[1] describing scalar electrocardiographic criteria for the concomitant presence of left anterior fascicular block and inferior wall myocardial infarction are encouraging to students of deductive electrocardiography and Grant's spatial vector method.[2] The diagnosis of inferior myocardial infarction with concomitant left anterior fascicular block by vectorcardiographic criteria is dependent on reversal of QRS loop rotation to counterclockwise beyond the 40 ms QRS instantaneous vector.[3] False positive electrocardiographic diagnoses of left anterior fascicular block in patients with only inferior myocardial infarction by vectorcardiography may occur with the criteria proposed[1] because loop rotation—a vectorcardiographic criterion for left anterior fascicular block—cannot be easily translated into routine scalar electrocardiographic terms.

I have observed patients whose studies satisfied quantitative vectorcardiographic criteria for inferior myocardial infarction[4] who have left axis deviation on electrocardiography, a terminal positive deflection (r wave) in lead aVR, a terminal negative deflection (S wave) in leads II and aVF and whose entire QRS loop in the frontal plane on Frank vectorcardiography rotates clockwise (Fig. 1 and 2)! All of these persons had morphologic QRS complexes in leads II and aVF although mean and maximal amplitude QRS vectors were all negative and less than 25°, respectively, in the frontal plane.

Deductive electrocardiography, such as that utilized by Fisher et al. in the formulation of their "hypothesis," would have predicted that in all these persons the depth of the S wave should have exceeded that of the Q wave in the complexes of lead II. By similar reasoning, an RSr′ rather than an rSR′ or QR complex should have occurred in lead aVR, allowing differentiation of such troublesome cases. Neither of these hypotheses was dependably correct, probably because of the assumptions inherent in the hexaxial reference system as defined by the Einthoven triangle. The standard and augmented limb leads are not pure "frontal plane leads," as torso studies have revealed.[5]

What appears to be valid, however, is that in those cases with a false positive diagnosis of left anterior fascicular block by the electrocardiographic criteria of Fisher et al., the width (duration of inscription in the vectorcardiogram) of the Q wave in leads II and aVF is greater than that of the terminal S wave in these leads (Fig. 1). This would appear to occur only when QRS loop rotation in the frontal plane beyond the 40 ms vector remains clockwise (Fig. 2). Perhaps the criteria recently published for concomitant left anterior fascicular block should be further revised to exclude such rare cases by imposing the further restriction that the "deep terminal S wave in lead II must be wider than any preceding Q wave in that lead."



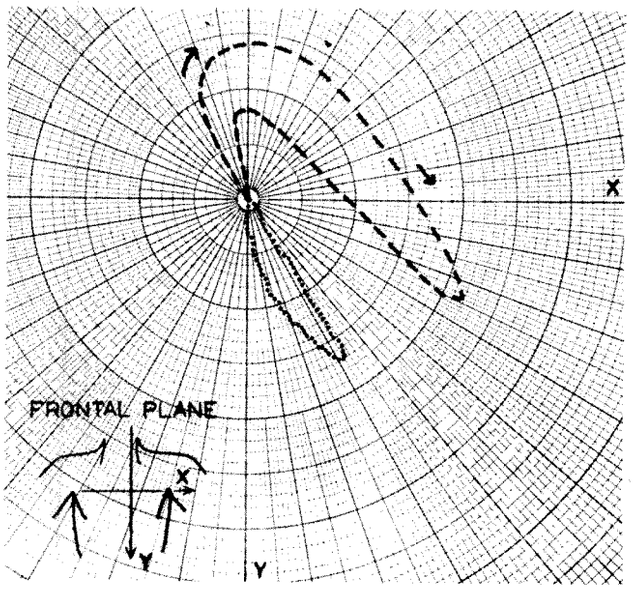


FIGURE 1 (top) and **FIGURE 2 (bottom).** See text for discussion.

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REPLY

It should be emphasized that the false positive pattern illustrated is relatively *rare*. Zema's suggestion of using both width and depth criteria for analyzing the terminal S wave in lead II should help to make our proposed criteria more specific. Total specificity cannot be anticipated until there are well established and unequivocal standards for the recognition of left anterior fascicular block.

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ELECTROCARDIOGRAPHIC PSEUDOINFARCTION PATTERN WITH PERICARDIAL EFFUSION

Salem and colleagues[1] described two patients with a large posterior pericardial effusion associated with electrocardiographic Q waves that disappeared after clearance of pericardial fluid. Although myocardial infarction was excluded in each case no precise explanation could be offered for the phenomenon but it was thought that changes in electrical conductivity and orientation of the heart within the pericardial sac in the presence of pericardial fluid might be responsible. These two cases were apparently the first reported illustrated examples of the occurrence of Q waves in this situation.

These two cases reminded me of a not dissimilar case that Levison and I[2] reported in 1976.

Case report: A 14 year old Scottish boy was found to have a large heart shadow on a chest radiograph taken because of contact at school with a child with tuberculosis. A presumptive diagnosis of tuberculosis pericardial effusion was made and he was admitted to the hospital. His symptoms were dry cough, retrosternal discomfort, anemia and occasional vomiting during the preceding week only. The electrocardiogram on admission is shown in Figure 1, top. Treatment with rifampicin, ethambutol and isoniazid was begun but on the 6th day after admission he became dyspneic and cyanosed. Cardiac tamponade was apparent clinically. One liter of blood-stained pericardial fluid was aspirated using an anterior approach. Within hours of aspiration the patient's condition deteriorated.

A second electrocardiogram revealed Q waves in leads I, aVL and V_2 to V_3 (Fig. 1, bottom). In the belief that further hemopericardium may have been induced by needle trauma during aspiration, a further aspiration was attempted and 300 cc of sanguinous pericardial fluid was aspirated with no clinical benefit. The patient died 10 hours after the initial aspiration despite attempts at resuscitation.

The case was of particular interest because the patient proved at necropsy to have a primary angiosarcoma of the right atrium and was younger than any previously reported patient with this finding. Moreover, histologic study showed the sarcoma to be of the Kaposi type. The electrocardiographic changes, although mentioned, were not illustrated in the paper. There was no evidence of coronary occlusion at necropsy and I believed the electrocardiographic changes were

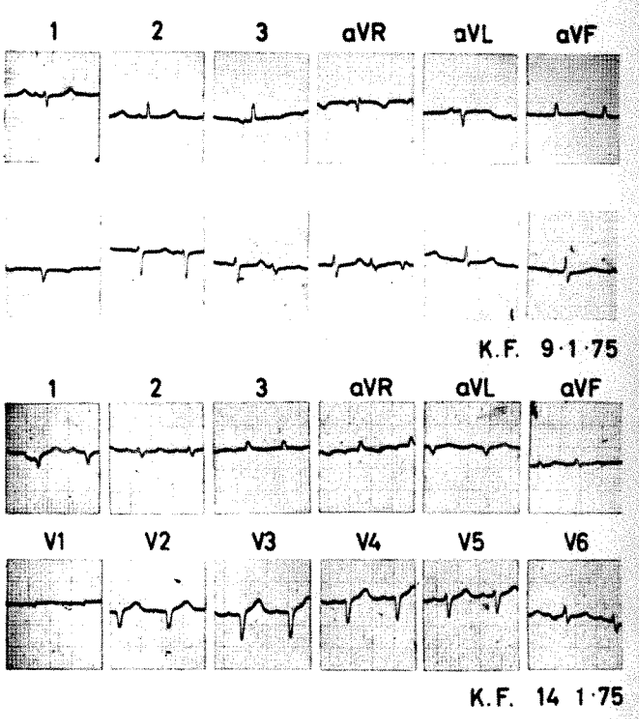


FIGURE 1. Electrocardiograms. **Top,** on admission to hospital when patient presented with pericardial effusion. Appearances are normal apart from some multifocal ectopic complexes. **Bottom,** after aspiration of one liter of pericardial fluid showing development of Q waves in leads I, aVL and V_2 to V_3.

probably due to major positional changes incurred by the removal of 1 liter of pericardial fluid. The electrocardiographic changes in this patient are very similar to those of Patient 1 of Salem et al. Interestingly, whereas in the American cases, Q waves disappeared after aspiration, in the Scottish case Q waves developed after aspiration. Unlike the American patients our patient had an extensive and not a localized posterior effusion.

Being a respiratory physician rather than a cardiologist I would not presume to offer explanations for the development of Q waves with pericardial effusion. However, I trust that Salem and associates will be interested to read of my case and will not be aggrieved if I proffer that the association had previously been noted.

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REPLY

We were interested to learn of this case, and not aggrieved by the claim that the association of Q waves and pericardial

effusion had previously been noted, because it is inaccurate.

In their description of the electrocardiographic changes Levison and Semple stated: "By this time Q waves had developed in the chest leads V1–V4 of the electrocardiogram, suggesting coronary occlusion as another possible cause of enzyme rise." Nowhere in the discussion is the possibility of the effusion being responsible for the Q waves mentioned; the electrocardiographic changes occurred after a traumatic pericardiocentesis and, even though coronary occlusion is implied, there is no description of the coronary arteries in the anatomopathologic report.

The context of the letter submitted to you is clearly different from that of the article. If in retrospect Semple believed that the electrocardiographic changes were probably due to major positional changes incurred by the pericardiocentesis, he failed to discuss it in his article.

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DRAINAGE OF PERICARDIAL EFFUSION

The exchange of letters over "medical" vs. surgical drainage of pericardial effusion by Becker, Achuff and Wei[1] sheds considerable light on the approach to management of a first class emergency—cardiac tamponade. I have been doing pericardial catheterization drainage for over 20 years[2–4] and, although in two cases a ventricle was entered, I have been fortunate to have had no mishaps (although an occasional "dry tap"). This may be due to luck or to the prevalence of very large effusions, which are easier to drain. I also prefer to aim for the left rather than the right shoulder and to proceed in a very slow, worm-gear motion as outlined elsewhere.[5]

I think all points made by both "opponents"[1] are valid and that, despite my own good luck, a limited subxiphoid surgical approach is probably optimal. When one does not have sufficient time and the situation is deteriorating rapidly, a needle pericardiocentesis must be done. I would only plead that the catheterization technique be used always, because once you are "in," a relatively soft catheter rather than a hard needle is pointed at the heart. On the other hand, I must disagree strongly with Becker's citation of the report by Kilpatrick and Chapman[6] as providing competent evidence. This was, indeed, an interesting, largely historical account. That part of it from their personal experience involved only 12 cases, in which the only death occurred in a patient with malignant invasion of the pericardium immediately after instillation of nitrogen mustard into the pericardial space—certainly not a complication of the tap itself. The authors make the incomprehensible statement: "Probably most attempts at pericardiocentesis have gone unrecorded unless they provide diagnostic information of dramatic input. Unsuccessful attempts, and not infrequently complications, may also fail to find their way into hospital records."[6] Plainly, this will not do. It is conjecture and not supported by a scintilla of evidence. Routine practice in any decent hospital is to record and note the details of all procedures. This is surely the standard in teaching hospitals and the report of Kilpatrick and Chapman is from a teaching hospital. In any case, even these authors agree to pericardial puncture when "time is of the essence." Moreover, large effusions are relatively easy to tap and should provide no difficulties for those willing to apply the exquisite care and patience necessary to avoid mishap.[5]

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POSTOPERATIVE CONSTRICTIVE PERICARDITIS

In their report of three cases of constrictive pericarditis after myocardial revascularization Marsa and colleagues[1] present well formulated conclusions regarding the role of povidone-iodine solution (Betadine®). In light of the appearance of these cases after the routine use of Betadine, it was reasonable to assign it a role in producing constriction. Previous work supports the role of the iodine moiety of Betadine. At least 28 agents or procedures have been employed to cause experimental pericardial scarring.[2] These data include the early work of Beck and Moore[3] and Musser and Herrmann,[4] who used iodine tincture to produce pericardial adhesions.

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REPLY

We appreciate Spodick's considerate and informative observations. Also we wish to draw attention to Cohen and Greenberg's report[1] of postoperative constrictive pericarditis, published after submission of our manuscript.

Two additional cases of surgically confirmed postoperative constrictive pericarditis have been seen by our group: *Case 1:* Nine months after an uncomplicated pulmonary commissurotomy performed in Saudi Arabia by members of our surgical team, an 18 year old Saudi Arabian youth presented with right heart failure (mean right atrial pressure 20 mm Hg)

and a right pleural effusion. He was successfully reoperated on in February 1979, with decortication of very adherent, densely fibrous tissue encompassing the heart and adjacent great vessels. It is not known whether he had had intraoperative pericardial irrigation with povidone-iodine solution at the time of his original operation. There was no evidence of tuberculosis.

Case 2: In a 9 year old Korean girl with tetralogy of Fallot, bilateral pleural effusions developed 10 days after corrective surgery performed at this institution in January 1980. She was afebrile. Increasing evidence of right heart failure led to cardiac catheterization (intracardiac diastolic pressures were approximately 20 mm Hg) and to surgical exploration 4 weeks postoperatively. Surgery revealed loculated pericardial fluid with a severely adherent pericardium, which was removed anteriorly. Recurrent right heart failure and pleural effusions led to reexploration 5 days later, with discovery of a newly formed, dense epicardial peel. Decortication was followed by immediate improvement in the patient's hemodynamics and a subsequently uncomplicated course. Histologically the surgical speciman showed dense fibrosis and areas with possible talc crystals and foreign body giant cells. The pericardium had not been irrigated with povidone-iodine.

The addition of these two cases to previously reported cases of constrictive pericarditis after cardiac surgery gives a total of 19. It is possible that as awareness of this entity increases it may prove to be more frequent than previously thought.

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Reference

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JUNCTIONAL ECTOPIC TACHYCARDIA IN INFANTS

I have been treating an 8 month old male infant with junctional ectopic tachycardia whose clinical course contrasts sharply with that of the patients described by Garson and Gillette.[1] The infant had an uneventful gestation and a normal spontaneous delivery. At age 2 days his heart rate ranged from 200 to 230 beats/min. An electrocardiogram (Fig. 1) demonstrated junctional tachycardia with occasional capture beats. Neither digitalization nor administration of propranolol (3 mg/kg daily) altered the rhythm. The infant was discharged from the hospital without medication. Although he had continuous junctional tachycardia, he remained asymptomatic and grew normally until age 3 months when he was hospitalized for an elective inguinal herniorrhaphy. Premedication was not given; anesthesia was induced with halothane by mask. While being intubated he manifested ventricular tachycardia (rate 240 beats/min). He was immediately given 100 percent oxygen, and the arrhythmia reverted to junctional tachycardia in about 15 seconds. Induction of anesthesia with halothane was again attempted, and ventricular fibrillation developed. After defibrillation with 50 watt seconds of direct current, the arrhythmia reverted to junctional tachycardia. The patient has had no further surgical procedures. When seen at age 8 months, his rhythm was unchanged; he was asymptomatic and growing normally.

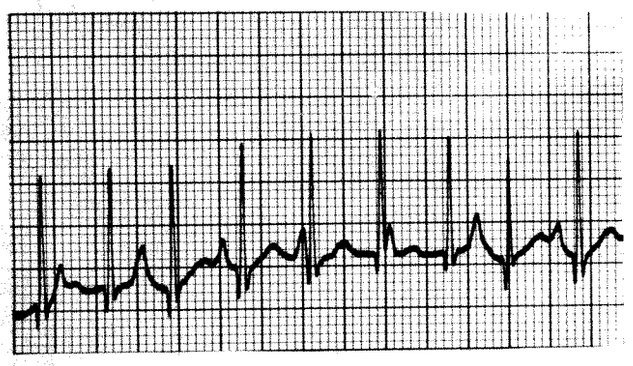


FIGURE 1. Lead II electrocardiogram obtained at age 7 months.

Although this patient's junctional tachycardia appeared to be benign, a dangerous arrhythmia developed under the stress of general anesthesia. I recommend premedication with propranolol and insertion of a temporary pacemaker before induction of general anesthesia in similar patients.

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Reference

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REPLY

Supraventricular tachycardias due to an ectopic focus are highly sensitive to sympathetic tone.[1] Pearl's patient demonstrated that during endotracheal intubation when sympathetic tone would most likely be high, either the junctional rate increased to 240/min with ventricular aberration or ventricular tachycardia developed. It would be impossible to distinguish between these two entities in the surface electrocardiogram, because each would have a prolonged QRS duration, with atrioventricular dissociation and possible fusion or capture beats. Halothane anesthesia is known to increase myocardial sensitivity to catecholamines and to decrease peripheral vascular resistance.[2] Ventricular fibrillation most likely developed because of the increase in sympathetic tone and increased sensitivity to catecholamines.

In managing Pearl's patient, we would further increase the propranolol dosage (up to 15 mg/kg daily). This dosage is usually well tolerated in children.[3] Our goal in therapy is to keep the heart rate in all patients at less than 150 beats/min. The development of cardiomyopathy in patients with chronic supraventricular tachycardia appears to be associated with more rapid heart rates.[1] We would have used an energy dose for defibrillation approximately one third of that used by Pearl. Assuming that a 3 month old infant weighs 4.5 to 5.4 kg, we would have used 10 to 12 joules for defibrillation. Gutgesell et al.[4] have established that the energy dose required for defibrillation in children is approximately 1 joule per pound. Since our report, we have had experience with three other patients, two of whom demonstrated the effects of increased sympathetic tone on junctional ectopic tachycardia. In the first patient, junctional ectopic tachycardia was noted soon after birth, and by age 8 months, although there was no other cardiac defect, the infant had chronic congestive heart failure. The rate of tachycardia was continuously higher than 250/min despite treatment with digoxin (0.01 mg/kg daily) and propranolol (18 mg/kg daily). On separate days, intravenous

phenytoin (15 mg/kg over 1 hour) and intravenous verapamil (0.15 mg/kg over 10 minutes) were given. Each resulted in a decrease in blood pressure and an *increase* in the rate of tachycardia. This was most likely due to a reflex increase in sympathetic tone caused by the hypotension. One week later, when the infant was undergoing endotracheal intubation for surgical ablation of the bundle of His and was anesthetized with halothane, ventricular fibrillation developed. After defibrillation, the bundle of His was successfully ablated by freezing, and a permanent ventricular pacemaker was implanted. The infant has been without junctional ectopic tachycardia for 3 months. He has entirely paced rhythm at a rate of 90/min.

The other patient, one of twins born with junctional ectopic tachycardia, also had mild hypotension in response to intravenous verapamil and had an increase in the rate of junctional ectopic tachycardia. The increased rate was reversed with intravenous calcium chloride, but the junctional tachycardia continued.

Therefore it appears that any agent that lowers blood pressure through either a decrease in systemic vascular resistance or a decrease in myocardial contractility may increase circulating catecholamines and increase the rate of junctional ectopic tachycardia. It is possible that phenylephrine with its attendant increase in vagal tone or calcium with its resultant increase in myocardial contractility might be successful acute treatment for junctional ectopic tachycardia in these situations.

We agree with Pearl that all patients with junctional ectopic tachycardia should receive propranolol before undergoing any surgical procedure. We would add that if the operation is elective, the patient should have a propranolol serum concentration greater than 40 ng/ml. A pacing catheter is not required for these patients. Bradycardia is unlikely and ventricular fibrillation will not respond to pacing. If the operation is performed as an emergency and the patient has not been receiving propranolol therapy, a pacing catheter should be inserted in the ventricle in case bradycardia develops, and propranolol, 0.1 mg/kg intravenously, should be given in four divided doses over 20 minutes before induction of anesthesia.

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ABSENT RIGHT SUPERIOR VENA CAVA

Lenox et al.[1] attempted a review of all published cases of absent right superior vena cava; however, they overlooked the two cases reported by Marin-Garcia et al.[2] Both cases were recognized before operation (correction of coarctation of aorta in one and closure of an atrial septal defect under cardiopulmonary bypass in the other). Although Lenox et al. comment on certain problems that this anomaly may pose during cardiac surgery, it is important to emphasize those situations where the diagnosis of absent right superior vena cava is mandatory: for instance, when an associated cardiac defect has to be repaired using cardiopulmonary bypass. In this situation, in addition to cannulation of the inferior vena cava, cannulation of the left superior vena cava is necessary, which can be accomplished by way of the coronary sinus, which is usually very dilated. A Glenn procedure may be indicated in patients with cyanotic congenital heart disease and decreased pulmonary blood flow. In this situation absence of the right superior vena cava requires that anastomosis be carried out in the left side. When a Mustard procedure is indicated in patients with transposition of the great arteries, attachment of the interatrial baffle might be different if the right superior vena cava is absent. As Lenox et al. point out, this anomaly may be less rare than previously thought. The diagnosis can be accomplished by means of cardiac catheterization and angiocardiography.

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REPLY

I apologize for omission of the two cases of absent right superior vena cava reported by Marin-Garcia et al.

In our review we did emphasize the importance of diagnosing absent right superior vena cava, both because of problems with cannulation at the time of surgery and because of the increased likelihood of conduction system abnormalities in the older patient with this entity. In cyanotic as well as noncyanotic heart disease, it is important to identify the presence of the right superior vena cava as well as persistent left superior vena cava. However, if augmentation of the blood supply to the pulmonary artery is needed, a Glenn procedure is rarely indicated.

In patients with transposition of the great arteries undergoing a Mustard procedure, the left superior vena cava would have to be cannulated. In cannulation of the left superior vena cava I again referred to Bosher,[1] who suggested that the cannula be advanced up the cava until its tip lies just inside the pericardium, thus decreasing the possibility of trauma to the conduction tissue in the area of the large coronary sinus. In performing the Mustard operation it is necessary to divert the large coronary sinus flow to the left-sided atrium and ventricle. This should be done cautiously because the conduction tissue extending from the atrioventricular node around the coronary sinus would be vulnerable to trauma.

I take this opportunity to add the case of unilateral left superior vena cava described by Holmes,[2] which was on the original list of cases to be included and was inadvertently left out. With the addition of these three cases there are 71 known cases at the present time.

It is hoped that, in time, more people will report their series. We would like to make a plea for electrophysiologic evaluation at the time of cardiac catheterization or microscopic study of the conduction system on postmortem material. In a future publication we will be reporting on the pathologic studies of

the conduction system in our two postmortem cases (Cases 1 and 2).

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NONINVASIVE MEASUREMENT OF VENTRICULAR PRESSURE—I

Since the recent publication of our paper[1] on noninvasive measurement of ventricular pressure throughout systole, we have discovered two important and relevant publications.[2,3] Using the Navier-Stokes equation, these authors developed an equation for deriving aortic blood velocity from a continuous recording of aortic pressure. In our paper, we derived pressure from a left ventricular volume-time curve obtained by nuclear techniques, using the basic equation:

$$dP/dt = \rho v \gamma$$

They derived the equation:

$$dP/dt = \rho c \gamma + acv.$$

(dP/dt is the first derivative of the pressure, ρ is density of blood, v and γ are velocity and acceleration of the ejected blood, c is the pulse wave velocity, a is a constant.) The major differences between their approach and ours are: (1) They did not assume, as we did, that the velocity of the pulse wave equals the velocity of the blood; and (2) they introduced the term, acv, that accounts for friction. Their data support the validity of their equation, as do our recent experimental data.

In three dogs we examined the relation between the left ventricular time-activity curve obtained with a camera computer system and the changes in aortic root pressure measured with a catheter. In each dog the chest was opened and a calibrated electromagnetic flowmeter was placed around the aortic root; and a pressure transducer was introduced into the carotid artery, and with fluoroscopy was placed as close to the aortic valve plane as possible. We waited 4 days for recovery from the thoracic surgery and stabilization of the baseline of the flow tracing. Gated equilibrium radioventriculography with the dog in a 40° to 50° left anterior oblique position was performed together with pressure and flow recordings on an oscilloscope, at rest and under pharmacologic changes induced by dibenzylline or propranolol. Each dog received 15 mCi of technetium-99m human serum albumin intravenously. We obtained a left ventricular time-activity curve integrated over 6 minutes of acquisition. Ejection fraction (EF) was then calculated. A mean stroke volume (SV) was obtained from the flow tracing by analysis of 10 beats. The end-diastolic volume (EDV), calculated from the equation EDV = SV/EF, was used for calibration of the absolute volume-time curve. The area of the aortic opening was measured directly at postmortem examination. A calculated pressure tracing was derived using equation (5) of the publication. The pulse pressure ranged from 1 to 4 mm Hg in 12 experiments, instead of 20 to 40 mm Hg as recorded by the pressure transducer. These results can be interpreted as follows: Integration by parts of our equation gives the following result: $P - P_o = \frac{1}{2}\rho v^2$, which is the kinetic pressure. Kinetic pressure in the aorta had been measured and found to have values within a range similar to ours.[4]

Thus, we conclude that the shape of the ventricular pressure curve as a function of time can be derived from the ventricular volume-time curve throughout systole, but for calculation of absolute pressure, we also need a measurement of the pulse wave velocity. We are now exploring several approaches to the calculation of absolute pressure from the ventricular volume-time curve.

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NONINVASIVE VENTRICULAR PRESSURE MEASUREMENTS—II

In attempting to measure ventricular pressure indirectly from the time-activity curve of ventricular ejection, Bourguignon and Wagner[1] have provided a new twist to an old controversy. In the first half of this century, a major goal of cardiovascular research was to do the opposite—to measure ventricular ejection from aortic pressure.[2] Attempts to do so proved unrewarding, because of the difficulty in characterizing arterial properties, and so identifying the separate components of cardiac ejection and vascular response in the arterial pressure pulse.

The method of Bourguignon and Wagner suffers from the same fundamental defect. Pressure generated in the ventricle during systole depends not only on the pattern of ventricular ejection but also on arterial viscoelasticity and blood density (which determine pulse wave velocity) and on the location of arterial branchings and terminations (which determine wave reflection). Studies of pressure and flow patterns and of vascular impedance in experimental animals and in man[3,4] have provided evidence of strong wave reflection, and of consequent augmentation in arterial and left ventricular pressure during systole. Thus, pressure in the ventricle during systole depends not only on the centrifugal wave generated by ventricular ejection but also on the centripetal waves that result from wave reflection.

No allowance is made for wave reflection in the calculations of Bourguignon and Wagner, which are based on the premise (their principle 2) that force, and so pressure, in the aorta are generated solely by acceleration of blood into the aorta.

In view of this fundamental deficiency, it is difficult to foresee the method described as having any more value than the older techniques that attempted the converse—measurement of ventricular ejection from arterial pressure.

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REPLY

Our overall goal has been to measure both ventricular volume and pressure as a function of time, since this would make it possible to monitor ventricular work. As MacDonald[1] has stated, measurement of pulsatile flow can make as great a contribution to understanding of the physiology of the circulation as has measurement of pulsatile pressure. As he stated: "The creation of a flow of blood and its transport to and from the tissues is, after all, the purpose of the cardiovascular system. The accompanying pressure changes, although intimately related to the flow, are essentially of secondary interest." The greatest potential of nuclear techniques in cardiology is that for the first time they permit continuous monitoring of ventricular volume. On theoretical grounds it should be possible to derive the pressure pulse wave during systole from the ventricular volume-time curve, the velocity of the pulse wave at the opening of the aortic valve, and blood density. In 1956, Fry et al.[2] used a double lumen pressure transducer to measure the pressure pulse curve at two points in the ascending aorta. Starting with the Navier-Stokes equation, a general equation for hydrodynamic flow, they derived the equation $\Delta P/\Delta x = \rho\gamma + av$ (1), where $\Delta P/\Delta x$ is the pressure gradient between the two catheter openings; Δx, the distance between the openings; ρ, the blood density; γ, the acceleration of blood; a, a constant; and v, the blood velocity through the aorta. Fry et al. measured $\Delta P/\Delta x$, assumed ρ = 1.05 g/cm^3, obtained the value of a by assuming that flow was zero at the end of systole; and by integration of equation (1), he was able to derive v, the velocity of blood. In the same year Jones et al.[3] modified the method of Fry et al. so that a single lumen rather than a double lumen catheter could be used. Equation (1) of Fry et al. was modified by Jones et al. as follows: $dP/dt = \rho c\gamma + acv$ (2), where dP/dt is the first derivative of the pressure in the aorta; c, the velocity of the pulse wave; and the other terms as defined.

We have derived a similar equation using a different set of assumptions: $dP/dt = \rho c\gamma$ (3), where c is the pulse wave velocity; γ is the acceleration, the derivative of v, the velocity. We measure flow by nuclear techniques as the rate of emptying of the ventricle. Flow (F) is related to the velocity (v) of blood through the aortic valve opening by the equation: F = vA, where A is the area of the aortic valve opening.

O'Rourke is correct when he states that, in a sense, our goal is the opposite of that of others in the first half of this century in that we derive pressure from volume as they tried to derive flow from pressure. However, there are important differences in our theoretical as well as methodologic approaches. Where they used the pressure pulse contour technique, we use the ventricular volume curve and a new equation, related to that of Fry et al. and not to that of Remington and Hamilton to which O'Rourke refers. Remington and Hamilton used an aortic pressure pulse contour technique in which the pressure pulse contour was divided into intervals of 10 ms duration. This technique has not proved successful.

Our approach, being completely different from the pressure pulse contour method, does not suffer from the same problems. Our method describes the relation between pressure pulse, pulse wave velocity and blood velocity. Anything that changes one of the three variables alters the others according to equation (3).

A final point is that we do not question the existence of reflected waves, but many authors[4] have shown that these do not give detectable effects at the aortic opening.

At present we are trying various ways to measure the pulse wave velocity by nuclear techniques. If these are unsuccessful, we plan to combine the nuclear measurements of flow with Doppler measurements of blood velocity. MacDonald[1] showed that the mean blood velocity ($\bar{v}$), the velocity of the pulse wave (c), and the cross-sectional area (A) of the vessel are related together in the following equation $\bar{v}/c = \Delta A/A$. Knowledge of blood velocity (Doppler) and flow (nuclear techniques) would make possible the calculation of the velocity of the pulse wave.

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SITE AND FREQUENCY OF INFECTION IN PORCINE VALVE BIOPROSTHESES

Ferrans et al.[1] presented ultrastructural observations in four infected bioprosthetic valves removed 6 days to 28 months after implantation; the thin layer of fibrin demonstrated on the bioprosthetic cusps was predicted to be material of high infective potential. The glutaraldehyde-stabilized porcine valve heterografts are certainly denuded of endothelium after fixation and, when implanted, are naturally covered with a thin layer of fibrin.

Clinical observations do not agree with this microscopic finding. In our own low profile bioprosthesis series (293 cases: mitral valve replacement, 114; aortic valve replacement, 83; double valve replacement, 26; valve replacement + associated procedures, 40), there were 4 cases of prosthetic endocarditis (incidence 4 of 293; 1.3 percent) in the follow-up period between 1976 and 1979. Of the four patients, two died after mitral and aortic valve replacement, respectively, and two recovered after aortic valve replacement.[2,3] In contrast, in our series with the Björk-Shiley prosthesis (220 cases: mitral valve replacement, 108; aortic valve replacement, 112) the incidence rate of prosthetic endocarditis was 5 percent after aortic valve replacement, and 2.68 percent after mitral valve replacement in the 5 year follow-up period from 1971 to 1976.

The small incidence of bioprosthetic endocarditis in the low profile bioprosthesis series may be due to the intensive search for chronic sepsis foci (specially oral and urinary) before surgery. Preparation of the patients for valve replacement is carried out by our Cardiological Department. In addition, intensive postoperative treatment with a wide spectrum of

antibiotic agents is provided for about 8 days in patients who have received a prosthetic cardiac valve.

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REPLY

Navia and Liotta raise two separate, independent questions: the site of localization of infection in porcine valve bioprostheses and the frequency with which such infections occur. Our conclusion that infection in porcine bioprostheses is initially localized in the cusps is in agreement with the findings of Rossiter et al.[1] in a larger series of patients. Our suggestion that the fibrin layer covering the cusps of the bioprosthesis is the initial site of bacterial attachment is in agreement with observations made on animals with experimentally induced bacterial endocarditis,[2] in which interaction between bacteria and fibrin deposits in leaflets of natural valves (denudation of valve endothelium by trauma leads to formation of these fibrin deposits) has clearly been demonstrated. We have not stated that the layer of fibrin is material of "high infective potential" and we find no justification for the statement by Navia and Liotta that "Clinical observations do not agree with this microscopic finding."

No conclusions as to the actual incidence of infection of bioprostheses could be derived from our small series of patients; however, our paper's review of the several published series reveals an average incidence rate of 1.4 percent, which is similar to the rate of 1.3 percent reported by Navia and Liotta. More recently, other investigators have reported overall rates of infection of 1.7,[3] 0.88[4] and 0.85 percent in patients followed up for less than 1 year and 1.3 percent in patients followed up for more than 1 year.[5] The data presented by these investigators has not been expressed either in terms of patient-year linearized rates or in terms of early (less than 2 months) or late (more than 2 months) infection. Because of this, the differences in incidence of infection in these series of patients and in the patients with Björk-Shiley and porcine bioprostheses described by Navia and Liotta are difficult to evaluate. Rossiter et al.[1] reported a significantly greater ($p < 0.05$) incidence of early infection in bioprostheses (6 of 16 valves) than in Starr-Edwards prostheses (3 of 35 valves), but found a comparable overall (early plus late) rate of infection, and of mortality associated with infection, for these two types of prosthetic valves. All early infections in bioprostheses occurred in valves implanted in the aortic position. Rossiter et al.[1] reported linearized rates of infection of 2.2 percent and 0.1 percent for bioprostheses implanted in the aortic and the mitral position, respectively. The linearized rates of infection reported by Angell[6] in Angell-Shiley bioprostheses were 0.5 percent for patients with a mitral bioprosthesis, 0.5 percent for patients with an aortic bioprosthesis and 4.4 percent for patients with multiple bioprostheses. Magilligan et al.[7] considered porcine valve bioprostheses and mechanical valves to be equally resistant to infection.

Although the discrepancies between the linearized rates just cited for patients undergoing single valve replacement by a porcine bioprosthesis are relatively minor, it should be pointed out that the rates of infection in prosthetic cardiac valves depend on numerous factors in addition to the careful preoperative eradication of foci of infection. For example, narcotic addiction was considered a factor contributing to infection of the porcine valve bioprostheses in 4 of the 11 patients reported on by Magilligan et al.[7] and in 1 of the 4 patients described in our study.

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Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

OCTOBER THROUGH DECEMBER 1980

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OCT. 6-9 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Hilton at the Circle, Indianapolis, IN

OCT. 23-25 — **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Vasodilators, Calcium Antagonists, Balloon Dilatation, Non-invasive Diagnosis; Valvular Heart Disease; Hypertrophic Cardiomyopathy.** Stephen E. Epstein, FACC, director. Hyatt Regency Hotel, Washington, DC

OCT. 23-25 — **Clinical Decisions in Cardiac Surgery.** Stanley K. Brockman, FACC, Albert N. Brest, FACC and William S. Frankl, FACC, directors. Fairmont Hotel, Philadelphia, PA

OCT. 30-NOV. 1 — **Fourth Annual Seminar. Cardiology Update 1980.** William W. Parmley, FACC, director. Del Monte Hyatt House, Monterey, CA

NOV. 5-7 — **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. The New York Hilton, New York, NY

NOV. 29-DEC. 1 — **Advances in Heart Disease 1981.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 4-6 — **Two-Dimensional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director and Leonard S. Dreifus, FACC and Gerald M. Pohost, FACC, co-directors. The Franklin Plaza Hotel, Philadelphia, PA

DEC. 7-10 — **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multi-Disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 12-14 — **Cardiovascular Disease: Achievements and Challenges 1980.** Henry I. Russek, FACC, director, Sheraton Centre, New York, NY

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OCTOBER THROUGH DECEMBER 1980

Month/Dates	Program Director	Title of Program
Oct. 8–10	William W. Parmley, MD	**Update in Noninvasive Procedures for the Evaluation of Cardiac Disorders**
Oct. 15–17	Arthur D. Hagan, MD	**Update in Cardiovascular Techniques and Principles for the Technologist**
Oct. 20–21	Joseph K. Perloff, MD and William C. Roberts, MD	**Functional Anatomy of Heart Disease: Clinician and Pathologist**
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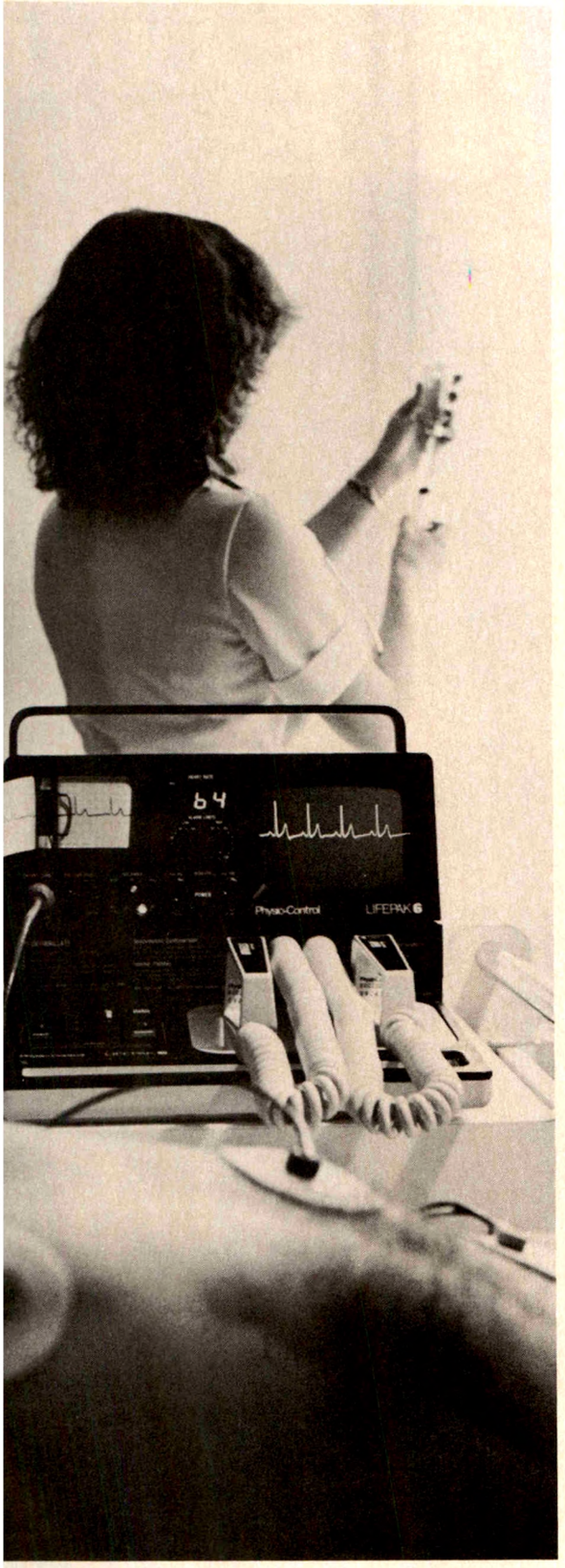
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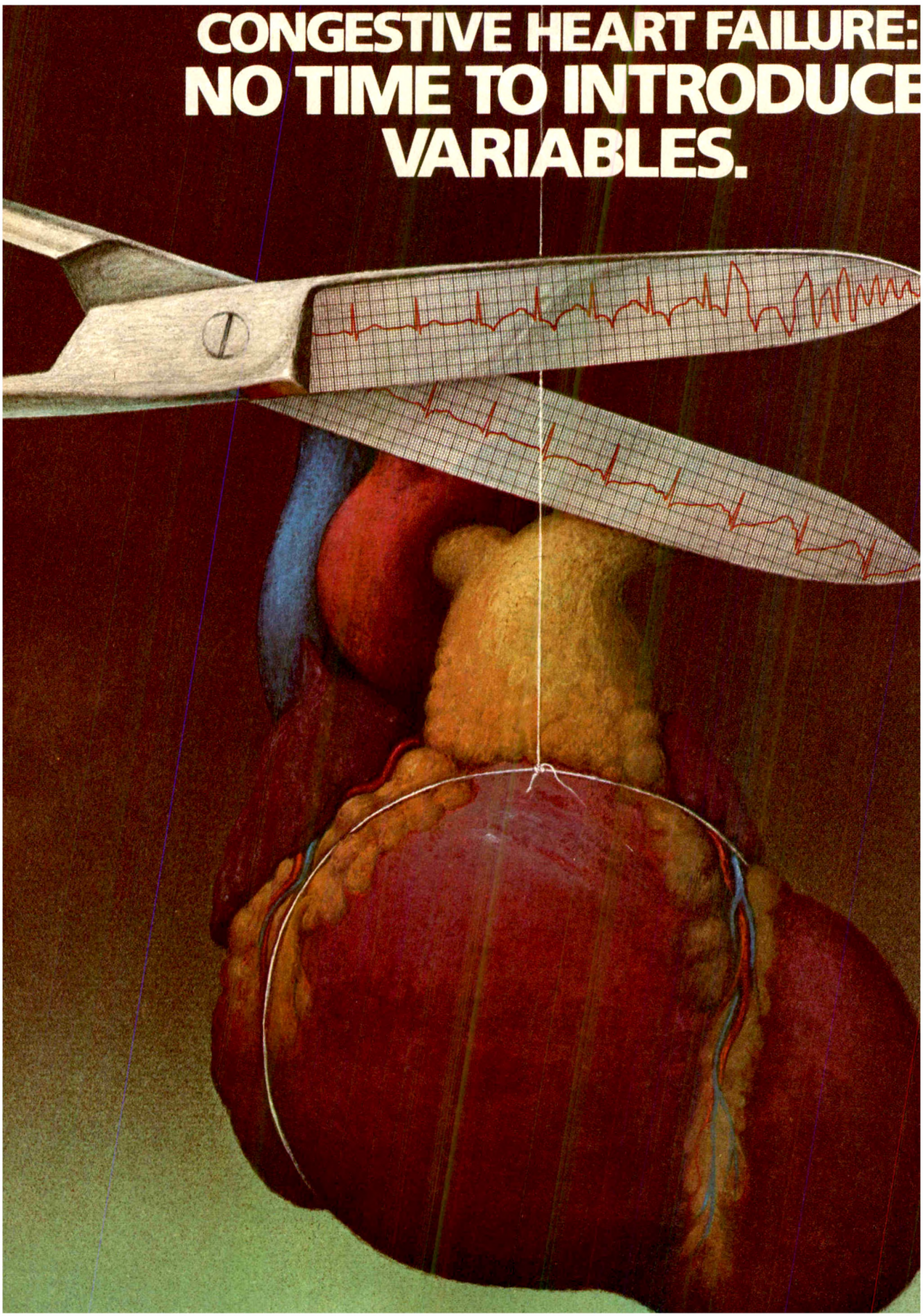
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INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter; and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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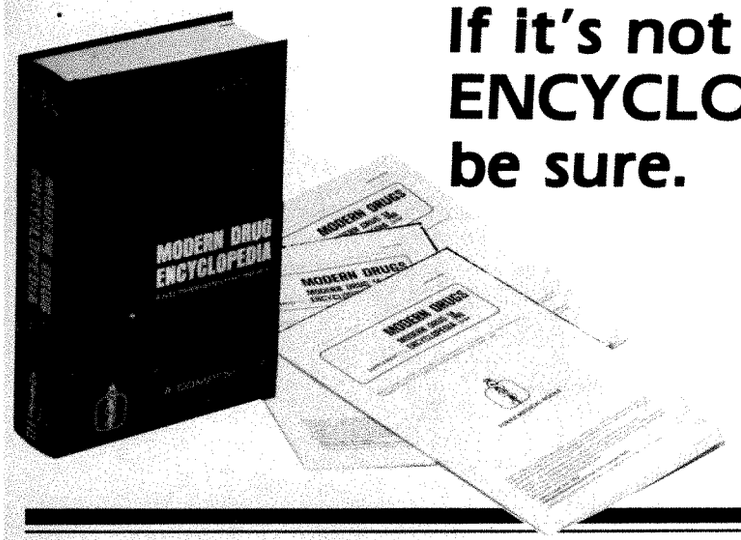
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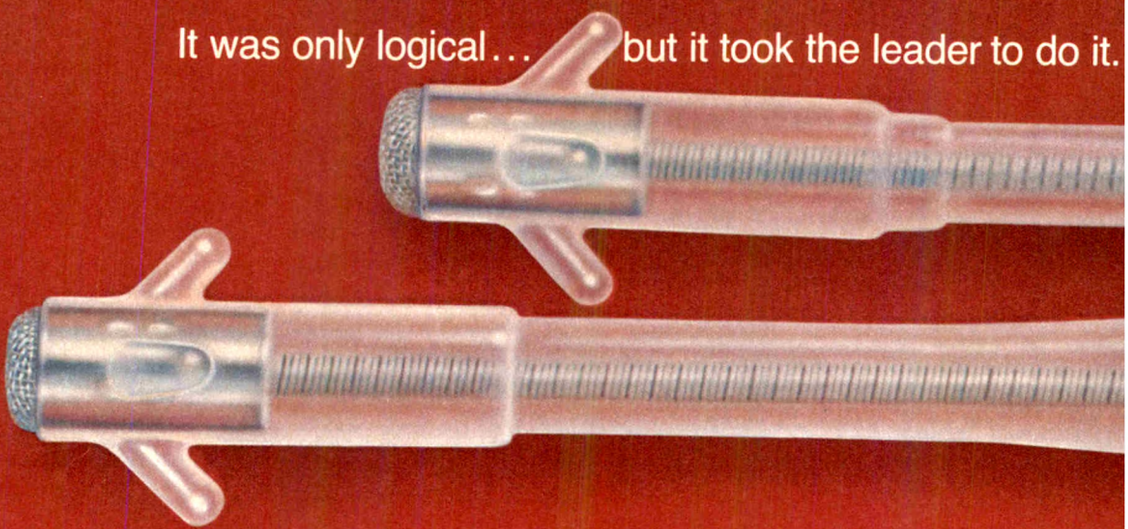
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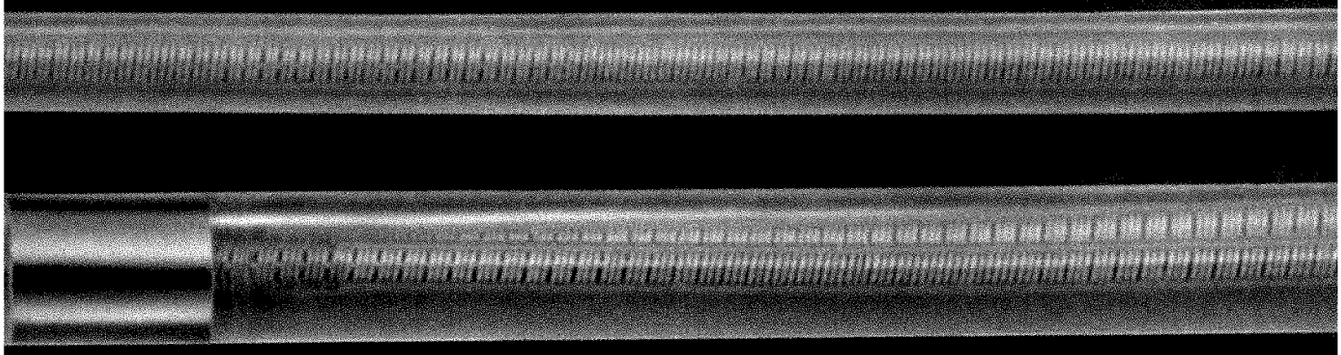
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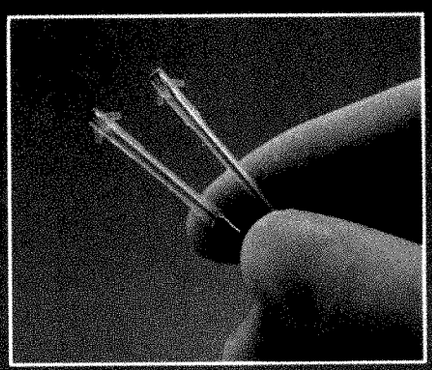
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INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

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Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

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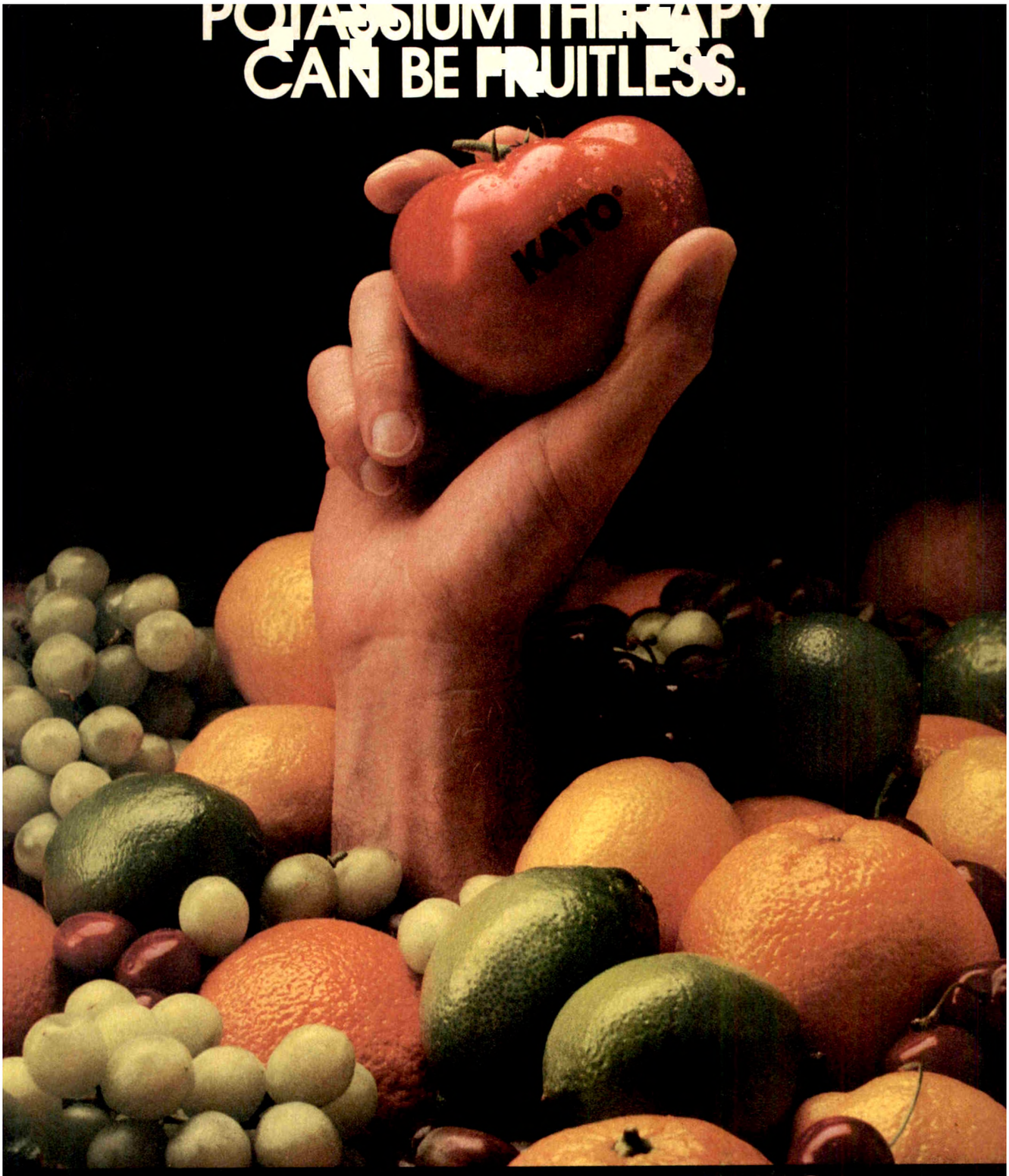
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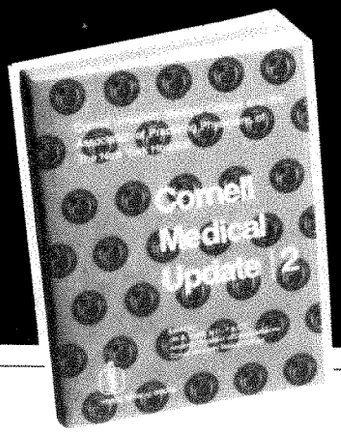
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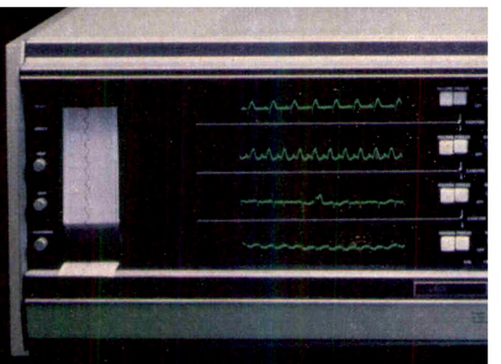
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Specifically, this expanded capability means accurate, on-line recognition of VPBs; reliable identification of dangerous arrhythmias; comprehensive data storage and retrieval facilities; quantitative drug response measurements; and a potential savings of time and money through the more efficient use of personnel[5].

If you've had doubts about the accuracy and effectiveness of computerized arrhythmia monitoring systems, take a look at the first computer-assisted arrhythmia IDENTIFICATION system. VIGILANT from B-D. It's a quantum leap ahead . . . for you, your staff and your patients!

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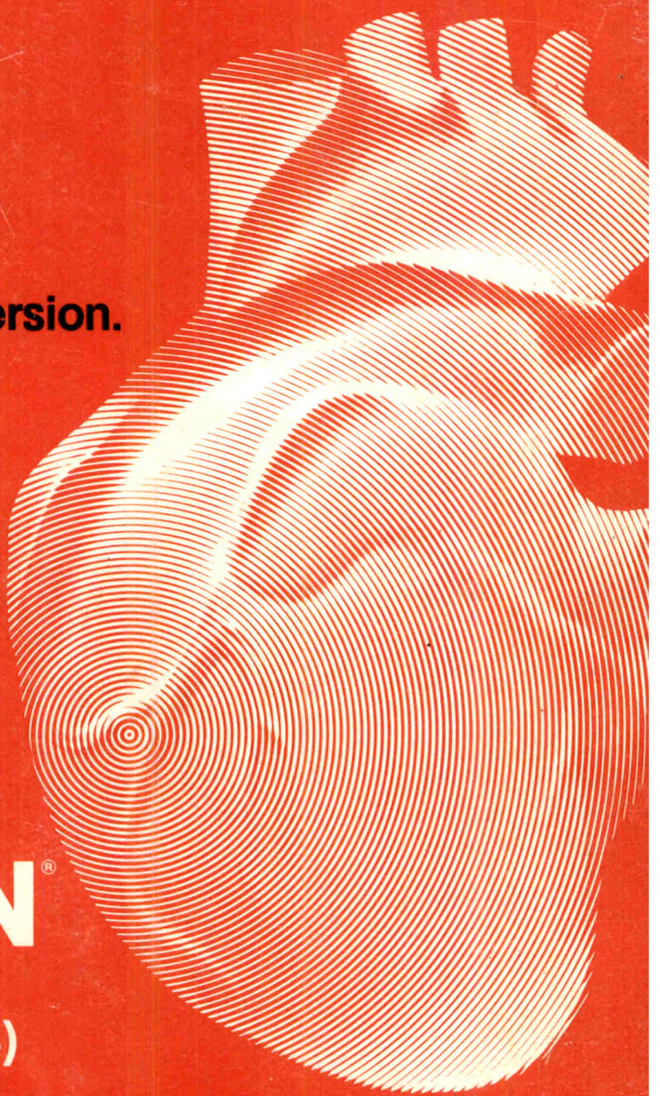
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Telephone: (617) 784-7878 or 1 (800) 225-0455 (outside Massachusetts)

See VIGILANT at the AHA, Miami Beach, Booth #L21.

1. Romhilt, D.W., et al: Unreliability of Conventional Electrocardiographic Monitoring for Arrhythmia Detection in Coronary Care Units. **American Journal of Cardiology** 31: 457-461, 1973.
2. Shah, P.M., et al: Automatic Real Time Arrhythmia Monitoring in the Intensive Coronary Care Unit. **American Journal of Cardiology** 39: 701-707, 1977.
3. Ibid.
4. Ibid.
5. Simson, M.B.: Computerized Arrhythmia Detection in Clinical Practice. Reprinted from "Symposium on


VIGILANT
Clinical Monitoring System

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For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

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TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quini polygalacturonate) are indicated in the treatment of: premature a and ventricular contractions; paroxysmal atrial tachycardia; paro mal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillat established atrial fibrillation when therapy is appropriate; paroxys ventricular tachycardia when not associated with complete he block; maintenance therapy after electrical conversion of atrial fi lation and/or flutter. CONTRAINDICATIONS: Aberrant impulses abnormal rhythms due to escape mechanisms should not be trea with quinidine. WARNING: In the treatment of atrial flutter rever to sinus rhythm may be preceded by a progressive reduction in degree of AV block to a 1:1 ratio and resulting extremely rapid v tricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quini polygalacturonate 275 mg.) is equivalent in quinidine content grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dos must be adjusted to individual needs, both for conversion and m tenance. An initial dose of 1 to 3 tablets may be used to termi arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhy is not restored after 3 or 4 equal doses, the dose may be increa by ½ to 1 tablet (137.5 to 275 mg.) and administered three to times before any further dosage increase. For maintenance, tablet may be used two to three times a day; generally one ta morning and night will be adequate. SUPPLIED: Uncoated, sco tablets in bottles of 100.

Purdue Frederick

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Calcific Deposits in Porcine Bioprostheses

Methodologic Problems in Exercise Testing

Pulsed Doppler Echocardiography in Cyanotic Newborns

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ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

Cardiac output and blood pressure normally increase with increasing physical activity. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[1,2]

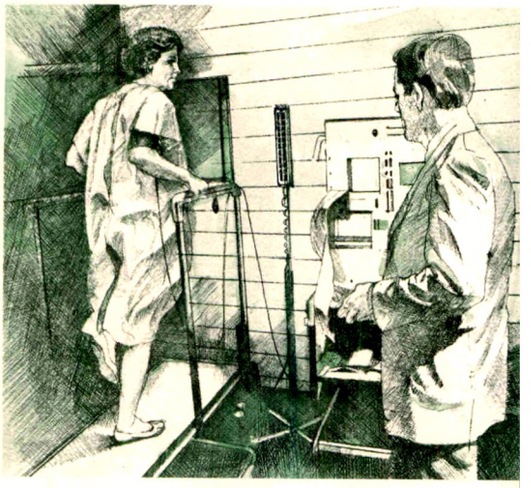
In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

Such findings can be of importance to active hypertensive patients such as the athletic individual or the person whose work requires substantial physical effort. For these and many other hypertensive patients, ALDOMET represents a logical therapeutic choice.

With ALDOMET, exercise hypotension rarely occurs. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

ALDOMET® offers many (METHYLDOPA|MSD) other important features:

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previ methyldopa therapy has been associated with liv disorders. It is important to recognize that a posit Coombs test, hemolytic anemia, and liver disord may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorde could lead to potentially fatal complications unle properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hyper tension by means of a graduated ergometric test, in Zanchet (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Clini Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 56-63.
2. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatm with methyldopa on basal hemodynamics and on neural cir latory control, in Zanchetti A (ed): ALDOMET® (Methyldo MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.
3. Lee WR, Fox LM, Slotkoff LM: Effects of antihypertensiv therapy on cardiovascular response to exercise. Am J Cardi 44:325-328, 1979.

For hypertension—

ALDOMET® The most prescribed nondiuretic antihypertensive in the U.S. tod
(METHYLDOPA|MSD)


TABLETS: 500 mg, 250 mg, and 125 mg
ALDOMET® WILL
(METHYLDOPA | MSD)
For a brief summary of prescribing information, please see following page.
MSD
MERCK SHARP & DOHME



For hypertension—

ALDOMET®
(METHYLDOPA|MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

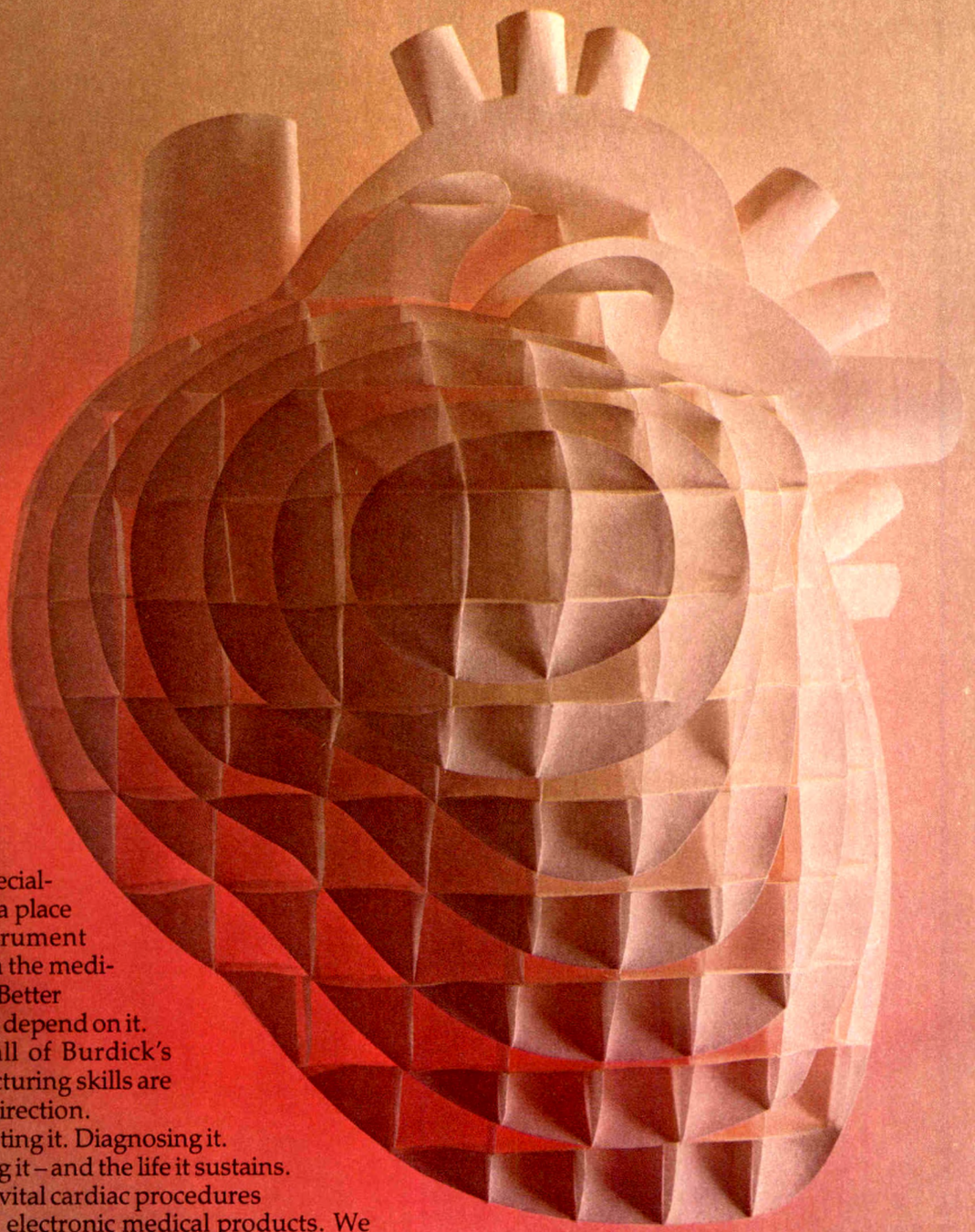
How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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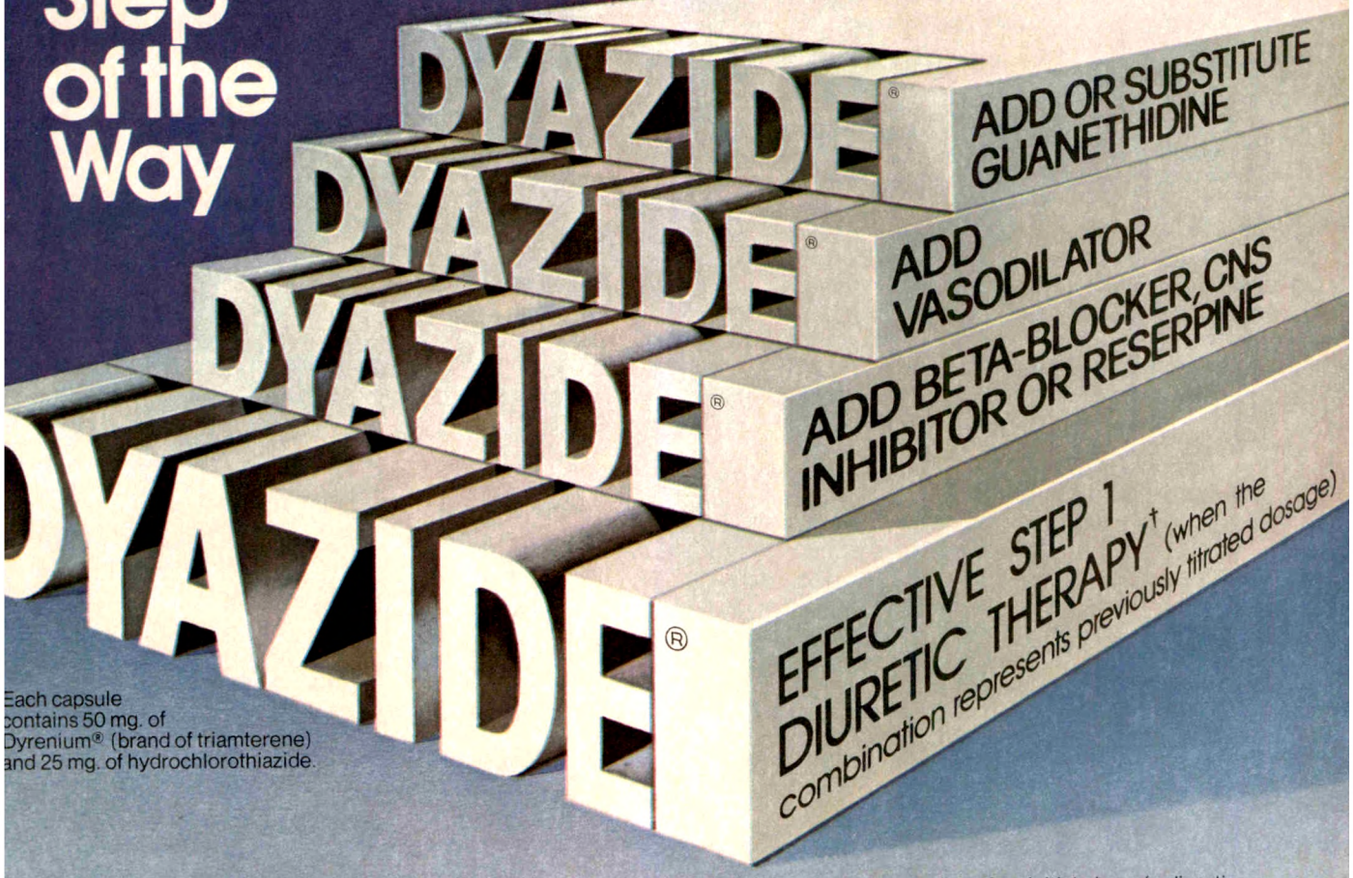
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Every Step of the Way



Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

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Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible bocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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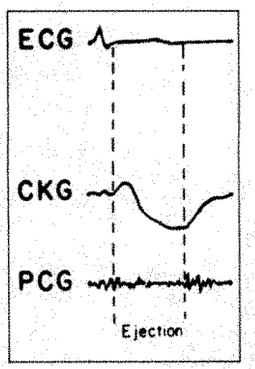


Fig. 2

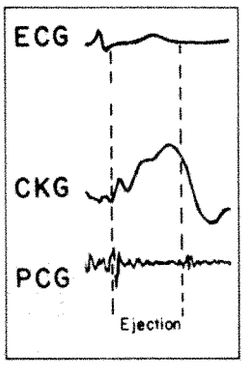


Fig. 3

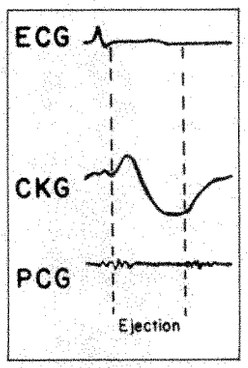


Fig. 4



I. Figure 1 is a pre-stress CKG™ (Cardiokymograph) tracing of the left ventricle (V3 position), it demonstrates:*

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

II. Figure 2 is a two minute post-stress CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

III. Figure 3 is a thirty minute post-stress resting CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

IV. Figures 1, 2 and 3, taken together, demonstrate:

- ☐ A. stress induced ventricular wall motion abnormalities consistent with ischemia
- ☐ B. normal ventricular wall motion

V. According to recently published[1] data, the CKG (Cardiokymograph) stress test is:

- ☐ A. 98% sensitive—98% specific
- ☐ B. 59% sensitive—69% specific
- ☐ C. 74% sensitive—95% specific
- ☐ D. 40% sensitive—60% specific

VI. Figure 4 is a photograph of:

- ☐ A. CKG/700 (Cardiokymograph)
- ☐ B. a noninvasive device that provides an analog representation of wall motion
- ☐ C. a low cost, simple device to be used in conjunction with stress testing to enhance diagnostic accuracy
- ☐ D. all of the above

REFERENCE

(1)Silverberg R A, Diamond G A, Vas R, Tzivoni D, Swan H J C, Forrester J S. Noninvasive Diagnosis of Coronary Artery Disease: The Cardiokymographic Stress Test. Circulation, Vol. 61, No. 3, pgs. 579-589

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QUICK QUIZ—ANSWERS

I. A normal systolic inward motion **II.** C holosystolic outward motion **III.** A normal systolic inward motion **IV.** A stress induced ventricular wall motion abnormalities consistent with ischemia **V.** C 74% sensitive—95% specific **VI.** D all of the above

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26790 A

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Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.
Precautions: Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE* (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.
Onset of Effect: Two to five minutes.
Duration of Effect: One to two hours.

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NOVEMBER 1980

The American Journal of CARDIOLOGY®

VOLUME 46

NUMBER 5

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CLINICAL STUDIES

721 Calcific Deposits in Porcine Bioprostheses: Structure and Pathogenesis

VICTOR J. FERRANS, STEVEN W. BOYCE, MARGARET E. BILLINGHAM, MICHAEL JONES, TOKUHIRO ISHIHARA and WILLIAM C. ROBERTS

Gross, histologic and ultrastructural analysis of 14 calcified porcine valve prostheses suggest that calcific deposits occur at all ages, but are usually more severe and clinically significant in children and young adults than in older patients. The calcific deposits limit the mobility of the cusps and may lead to prosthetic valve stenosis or regurgitation. The connective tissue in the cusps, particularly in the spongiosa, and small thrombi on the surfaces are the two main sites of such deposition of calcium phosphate. Calcification of connective tissue first involves the collagen fibrils; calcification of thrombi involves the mitochondria in platelets and leukocytes trapped in the mesh of fibrin. These deposits represent the results of different mechanisms that are discussed in depth.

735 Chronic Intravascular Hemolysis After Aortic Valve Replacement With Ionescu-Shiley Xenograft: Comparative Study With Bjork-Shiley Prosthesis

PEDRO R. FEBRES-ROMAN, WILSON C. BOURG, RICHARD A. CRONE, RICHARD C. DAVIS, Jr. and TROY H. WILLIAMS

This study of 20 patients with a prosthetic valve (Ionescu-Shiley or Bjork-Shiley) in the aortic position at a mean interval of 10.6 months after aortic valve replacement demonstrates a significantly greater incidence and degree of mild chronic intravascular hemolysis in the patients with the Ionescu-Shiley prosthesis than in those with the Bjork-Shiley prosthesis. The hemolysis appears to be related to the mechanical design of the prosthesis. No direct relation was found between serum lactic dehydrogenase or haptoglobin and valve size. It is also unlikely that an immune mechanism played a role. With time, endothelialization of the valve structures may lead to a lesser degree of erythrocyte destruction and hemolysis with the Ionescu–Shiley prosthesis.

739 Two Dimensional Echocardiographic Recognition of the Descending Thoracic Aorta: Value in Differentiating Pericardial From Pleural Effusions

WILLIAM S. HAAZ, GARY S. MINTZ, MORRIS N. KOTLER, WAYNE PARRY and BERNARD L. SEGAL

Using the location of the descending thoracic aorta on two dimensional echocardiography to differentiate pericardial from pleural effusions in 40 patients, these investigators found it constituted a valuable diagnostic aid. In this study 83 percent of the M mode studies were diagnostic in patients with a pericardial effusion. In 17 percent there was some difficulty in differentiating between a pericardial and pleural effusion. In these patients the location of the descending thoracic aorta on the two dimensional echocardiogram proved helpful. Combined pericardial and pleural effusions were visualized as echo-free spaces both anterior to and posterior and lateral to the descending thoracic aorta. The determination of the exact sensitivity and specificity of these findings awaits additional prospective study.

continued on page A16


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Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. (See product labeling for a complete list of warnings and precautions.)

Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

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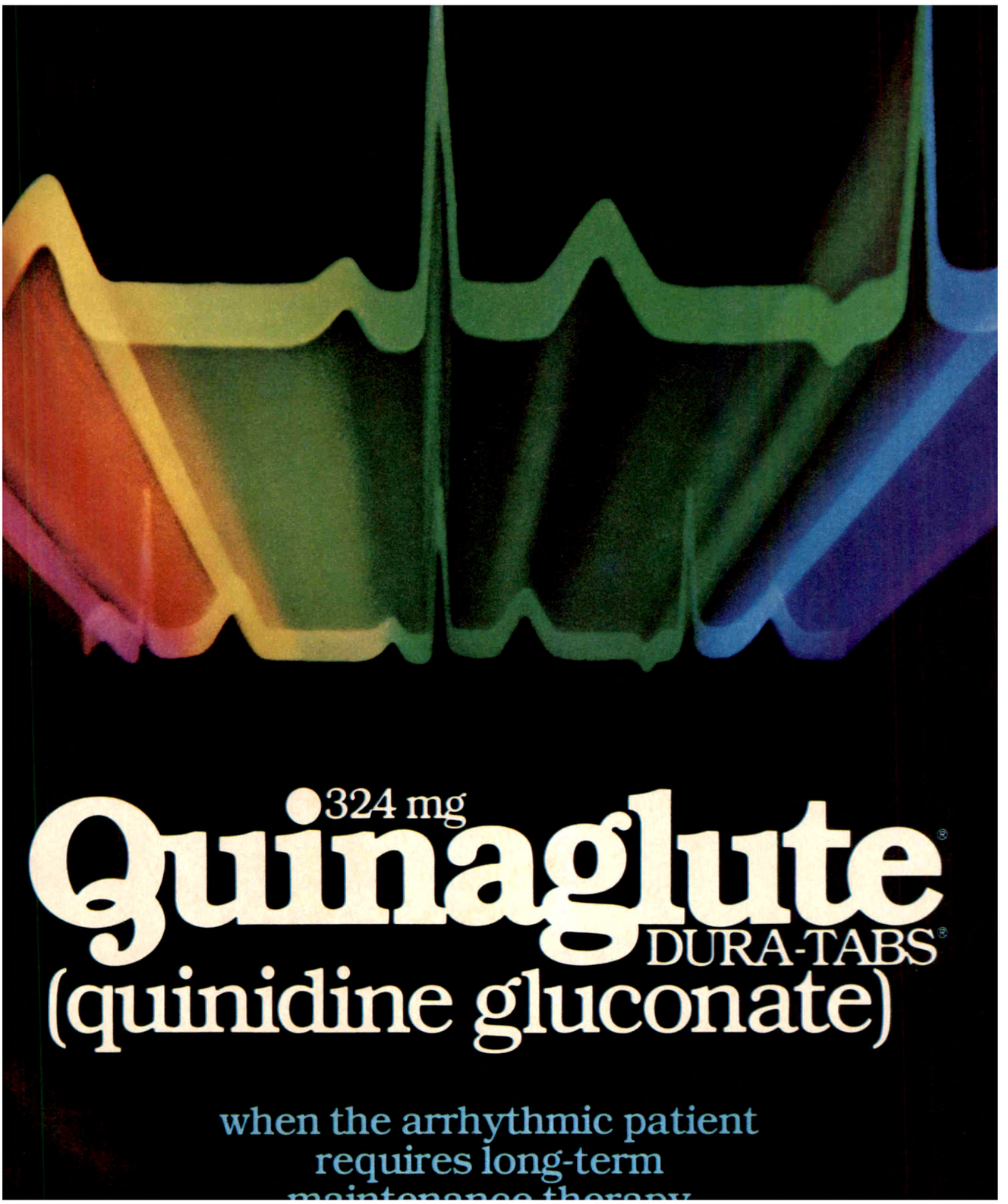
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Idiosyncrasy or hypersensitivity to quinidine.
WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.
PRECAUTIONS:
The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.
Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.
It should be administered cautiously, if at all, to senile patients.
Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.
ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.
Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision fields, photophobia, diplopia, night blindness, scotomata), optic neuritis.
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744 Histologic and Ultrastructural Features of Normal Human Parietal Pericardium

TOKUHIRO ISHIHARA, VICTOR J. FERRANS, MICHAEL JONES, STEVEN W. BOYCE, OICHI KANANAMI and WILLIAM C. ROBERTS

Histologic and transmission and scanning electron microscopic observations on normal human parietal pericardium indicate that the pericardial mesothelial cells of the serosa have single cilia and are covered with microvilli that bear friction and increase the surface area for fluid transport. Actin-like filaments (50 Å in diameter) in the microvilli and in immediately subjacent regions mediate change in cell shape. Intermediate filaments (100 Å in diameter) are associated with desmosomes, form bundles in the perinuclear regions, and provide structural support to the cytoplasm. The observations demonstrate the complexity of the organization of the various structural components of human parietal pericardium and illustrate the range of adaptations this tissue has developed to perform its functions. The connective tissue permits only a limited amount of stretch, which is mediated by straightening of the wavy arrangement of bundles of collagen fibrils.

754 True Left Ventricular Aneurysm and Healed Myocardial Infarction. Clinical and Necropsy Observations Including Quantification of Degrees of Coronary Arterial Narrowing

HENRY S. CABIN and WILLIAM C. ROBERTS

In this clinicopathologic study of 28 necropsy patients with left ventricular aneurysm it was found that the myocardial infarction is large, the nonscarred left ventricular wall is hypertrophied, the left ventricular cavity is dilated, and the major epicardial arteries are severely narrowed. Chronic congestive heart failure is frequent and the major cause of death, but chest pain, arrhythmia, recurrent myocardial infarction and systemic embolism are infrequent. The clinical diagnosis by means other than left ventricular angiography is infrequently made.

764 Response to Exercise Early After Uncomplicated Acute Myocardial Infarction in Patients Receiving No Medication: Long-Term Follow-Up

GERALD M. KOPPES, WILLIAM KRUYER, CHARLES H. BECKMANN and FREDERIC G. JONES

Submaximal treadmill exercise testing 3 weeks after an uncomplicated acute myocardial infarction in 90 patients on no medication proved safe and provided reference values for safe limits in performing maximal treadmill testing at 8 weeks after infarction. S-T segment changes or angina, or both, the inability to complete a maximal 8 week treadmill test identified patients at risk for later complications. Exercise variables at submaximal equivalent exercise work did not change from 3 to 8 weeks. At maximal exercise 15.6 percent of the patients had S-T changes alone, 8.9 percent had angina pectoris alone and 12.2 percent had both. In all, fatigue, progressive shortness of breath or leg discomfort rather than angina was the exercise end point. Modified treadmill testing at 3 weeks and maximal testing at 8 weeks after acute myocardial infarction under controlled circumstances are more safely performed than unmonitored home management and follow-up of such patients.

770 Improvement in Ventricular Function During Exercise Studied With Radionuclide Ventriculography After Cardiac Rehabilitation

DAVID JENSEN, J. EDWIN ATWOOD, VICTOR FROELICHER, M. DAN McKIRNAN, WILLIAM ASHBURN and JOHN ROSS, Jr. with the technical assistance of JUDY SASSONE, MARY LOU STRONG and JULIE FROELICHER

This study using radionuclide ventriculography to assess left ventricular function at rest and during exercise before and after a training program in 19 patients with coronary artery disease showed that after training the subjects achieved a higher maximal mean systolic blood pressure, heart rate and work load, but no change in mean ejection fraction at rest or during maximal exercise. At equivalent submaximal work loads after training, similar levels of mean heart rate and systolic blood pressure were reached and a statistically greater mean ejection fraction was obtained. Data in four patients with coronary bypass grafting also indicate exercise training benefited them. Since spontaneous improvement in function may follow a myocardial infarction, controlled larger studies are needed to document further these preliminary findings and to assess which patients respond most favorably to exercise training as a mode of therapy.

continued on page A22

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Reduction in heart rate is modest: should not be cause for concern.[7] The relatively low dosages required for angina prophylaxis (an average of 160 mg/day) produce few, if any, serious adverse reactions, which in any case are readily recognized and controlled.

With proper patient selection—in the absence of bronchial asthma, sinus bradycardia, or heart block greater than first degree—risk of precipitating cardiac failure is extremely rare. And withdrawal problems may be avoided by reducing dosage gradually—rather than abruptly.*

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® BRAND OF
PROPRANOLOL HYDROCHLORIDE
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis: The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCH EMPHYSEMA), INDERAL should be administered with caution since it may block broncho tion produced by endogenous and exogenous catecholamine stimulation of beta receptor

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrene blocking activity, INDERAL may prevent the appearance of premonitory signs and sympto (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to k in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a p cipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been es- tablished. Use of any drug in pregnancy or women of childbearing potential requires that t possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. bryotoxic effects have been seen in animal studies at doses about 10 times the maximum r ommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug then produce an excessive reduction of the resting sympathetic nervous activity. Occasion the pharmacologic activity of INDERAL may produce hypotension and/or marked bradyca resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be ob served at regular intervals. The drug should be used with caution in patients with impaired or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypoten paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, l tude, weakness, fatigue; reversible mental depression progressing to catatonia; visual dist bances; hallucinations; an acute reversible syndrome characterized by disorientation for ti and place, short term memory loss, emotional lability, slightly clouded sensorium, and de- creased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, c stipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with achir and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpu

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, s ous membranes and conjunctivae reported for a beta blocker (practolol) have not been co sively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe hear ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three or fo times daily, before meals and at bedtime, dosage should be gradually increased at three t seven day intervals until optimum response is obtained. Although individual patients may r spond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several wee (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit ade- quate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING M SURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPON TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

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No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 10 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 10 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The p adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

References: 1. Dagenais, G.R., Pitt, B., and Ross, R.S.: Am. J. Cardiol. *28*:10 (July) 1971. 2. Ginn, W.M., and Orgain, E.S.: J.A.M.A. *198*:192 (Dec. 12) 1966. 3. Zeft, H.J., Patterson, S and Orgain, E.S.: Arch. Intern. Med. *124*:578 (Nov.) 1969. 4. Dunér, H., and Pernow, B.: Act Med. Scand. *194*:517 (Dec.) 1973. 5. Zsoter, T.T., and Beanlands, D.S.: Arch. Intern. Med. *124*:584 (Nov.) 1969. 6. Wiener, L., Dwyer, E.M., and Cox, J.W.: Circulation. *39*:623 (May) 19 7. Shand, D.G.: Drug Therapy *8*:53 (July) 1978. 8. Cohen, L.S., in Braunwald, E. (ed): Beta-Adrenergic Blockade, A New Era in Cardiovascular Medicine: Proceedings of an Internatic Symposium, New York, Excerpta Medica/Elsevier, 1978, pp. 143-151.

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CONTENTS

778 Relation of Exercise-Induced Physiologic S-T Segment Depression to R Wave Amplitude in Normal Subjects

MYRON C. GERSON, STEPHEN N. MORRIS and PAUL L. McHENRY

Exercise electrocardiographic data obtained in 100 asymptomatic male volunteers with a mean age of 42.6 years demonstrated a significant relation between the magnitude of R wave and total RS amplitudes and the magnitude of physiologic S-T segment depression. These findings suggest a need to evaluate S-T depression corrected for R wave amplitude because the sensitivity and specificity of the exercise electrocardiogram may be improved by correcting the amount of S-T depression for the magnitude of R wave amplitude. Criteria for abnormal S-T depression should include consideration of the different R wave voltages in the different types of recording leads.

EXPERIMENTAL STUDIES

783 Continuous Fractionated Electrical Activity After Stimulation of the Ventricles During the Vulnerable Period: Evidence for Local Reentry

DAVID E. EULER and E. NEIL MOORE

Ventricular multiple extrasystoles and fibrillation were induced in open chest dogs by the delivery of a single electrical pulse or a train of pulses to the right ventricle during the vulnerable period of the cardiac cycle. The presence of continous local electrical activity before the development of multiple extrasystoles and fibrillation supports the thesis that the ventricular fibrillation threshold technique operates by producing local reentrant activity. The current required to produce continuous electrical activity and fibrillation with a train of pulses in this study was consistently less than that required for a single pulse. When continuous electrical activity disappeared during a run of extrasystoles, there was prompt resumption of normal sinus rhythm. Also, when such continuous electrical activity was produced by a single stimulus during the vulnerable period, it could be abolished by a second stimulus delivered during the protective zone.

792 Electrophysiologic Effects of Disopyramide Phosphate on Reentrant Ventricular Arrhythmia in Conscious Dogs After Myocardial Infarction

EUGENE PATTERSON, JOHN K. GIBSON and BENEDICT R. LUCCHESI

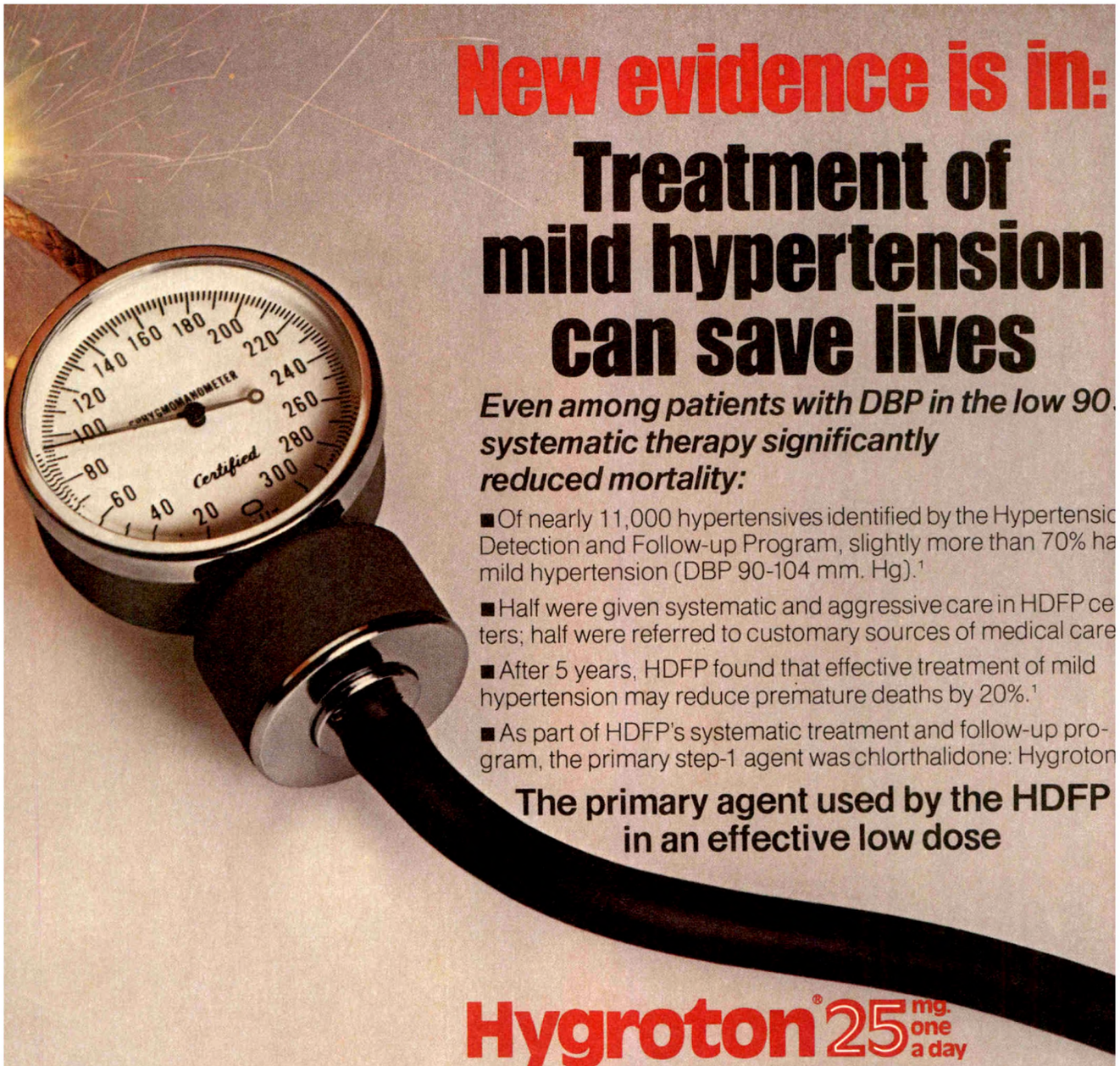
Evaluation of the electrophysiologic actions of disopyramide phosphate on reentrant ventricular tachycardia in conscious dogs 2 to 4 days after myocardial infarction demonstrates plasma therapeutic concentration in excess of the normal therapeutic range of 2 to 4 μg/ml are necessary to prevent ventricular tachycardia or fibrillation, or both. Lesser concentrations of 1.02 $\pm$ 0.02 μg/ml increased the rate and duration of ventricular tachycardia as well as the duration of the interval during which premature ventricular stimuli produced ventricular tachycardia. Subtherapeutic concentrations may facilitate the development of reentrant ventricular arrhythmia in the electrically unstable heart. There is evidence that plasma concentrations of antiarrhythmic agents necessary to prevent sudden coronary death may be higher than currently accepted "therapeutic" concentrations. However, the negative inotropic effect of disopyramide may preclude the use of higher dosage regimens in patients with compromised left ventricular function.

800 The No Reflow Phenomenon: A Time-Limiting Factor for Reperfusion After Coronary Occlusion?

JOHN R. DARSEE and ROBERT A. KLONER

The "no reflow" phenomenon, as analyzed in 33 dogs, does not determine the critical time for salvageability of infarcted myocardium by revascularization because the area of no reflow is surrounded by necrotic but reperfusable tissue. Reperfusion does not increase the quantity of ischemic tissue that becomes necrotic. The area of necrosis expressed as a percent of the area at risk was significantly smaller for dogs with 2 or 4 hours of occlusion and reperfusion than for dogs with longer periods of occlusion and briefer periods of reperfusion. The quantity of ischemic but still viable tissue is influenced primarily by the duration of the period between the onset of ischemia and the time of the intervention, and not by the existence, distribution or spatial geometry of the no flow phenomenon. Although the occurrence of the no reflow phenomenon in human subjects has not yet been determined, its presence could have important clinical implications for drug therapy and coronary bypass grafting.

continued on page A26



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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

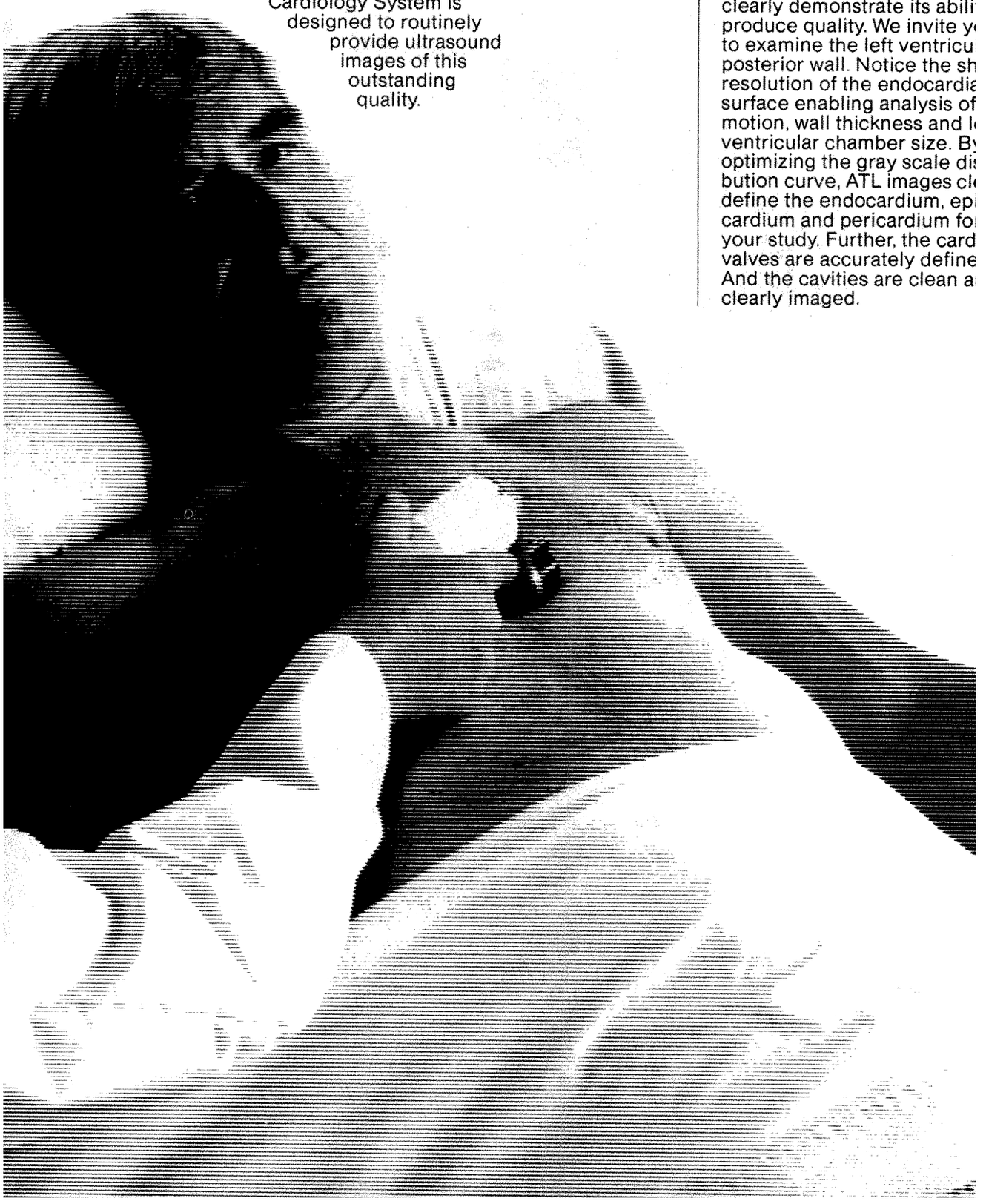
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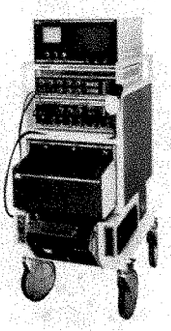
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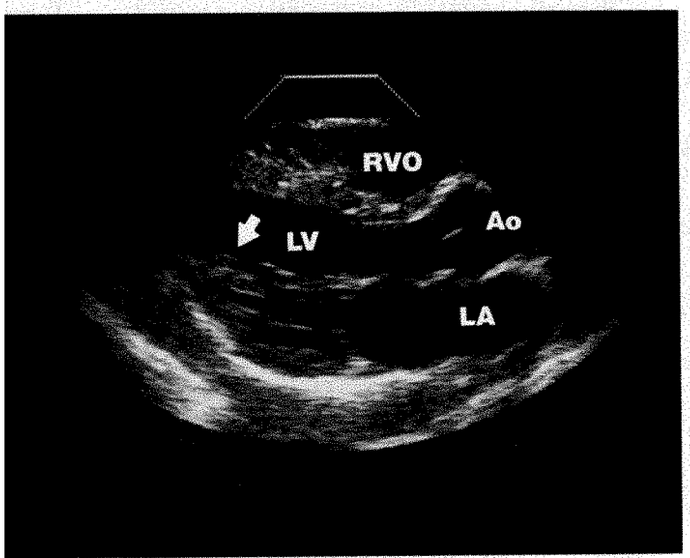
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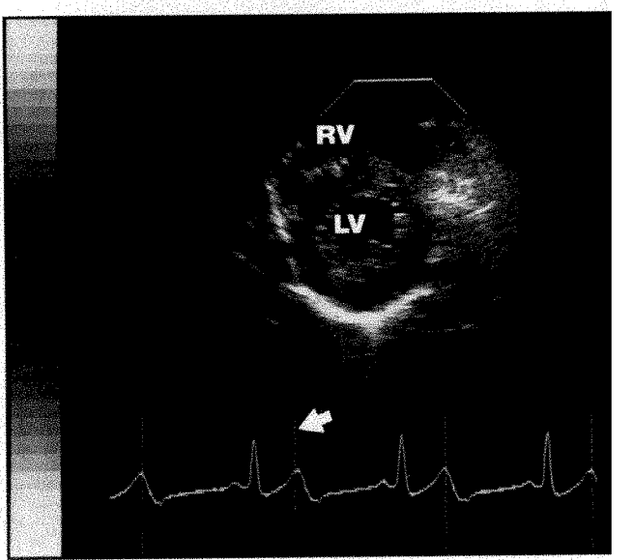


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Cardiology System



Long axis view, parasternal window. Slight medial angulation reveals papillary muscles (arrow).

LV=left ventricle. RVO=right ventricular outflow. Ao=aorta. LA=left atrium.



Short axis of left ventricle from parasternal window cursor-triggered freeze f

LV=left ventricle. RV=right ver Arrow=ECG

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CONTENTS

METHODS

807 Methodologic Problems of Exercise Testing for Coronary Artery Disease: Groups, Analysis and Bias

JOHN T. PHILBRICK, RALPH I. HORWITZ and ALVAN R. FEINSTEIN

Exercise testing remains controversial as a diagnostic test for coronary artery disease because of methodologic problems that produce a wide range of sensitivity (35 to 88 percent) and specificity (41 to 100 percent). In this review of 33 studies of 7,501 patients subjected to stress testing and coronary angiography, there was general compliance with only one of the seven standards used in this evaluation—adequate analysis of anatomic lesions. Less than half of the studies complied with any of the remaining six standards. The main conclusion is that exercise testing research should be made more clinically relevant. For this, investigators must pay greater attention to the basic methodologic design of patient selection, data collection and data analysis. But even with an improved basic design, the sensitivity and specificity of an exercise test may remain highly variable because the coronary arteriogram measures anatomic abnormalities whereas the exercise test measures the heart's physiologic response to increased work.

813 Peak Systolic Blood Pressure/End-Systolic Volume Ratio: Assessment at Rest and During Exercise in Normal Subjects and Patients With Coronary Heart Disease

ROBERT SLUTSKY, JOEL KARLINER, KENNETH GERBER, ALEXANDER BATTLER, VICTOR FROELICHER, GABRIEL GREGORATOS, KIRK PETERSON and WILLIAM ASHBURN

Using equilibrium radionuclide angiography to determine end-systolic volume and the systolic blood pressure obtained by cuff sphygmomanometer to determine peak systolic pressure these investigators found that the end-systolic pressure/volume ratio is a useful index of left ventricular performance. In some patients this ratio during supine exercise stress is more sensitive than the ejection fraction in identifying the presence of left ventricular dysfunction. The limitations of the method depend on the variability of the radionuclide technique and the accuracy with which the peak systolic blood pressure can represent the peak left ventricular systolic pressure. The noninvasive result tends to overestimate the actual ratio mainly because the brachial arterial pressure reflects an amplified left ventricular pressure wave secondary to the arterial compliance and pressure waveform of reflectance.

821 Influence of Coronary Artery Disease on Pulmonary Uptake of Thallium-201

JOHN B. BINGHAM, KENNETH A. McKUSICK, H. WILLIAM STRAUSS, CHARLES A. BOUCHER and GERALD M. POHOST with the technical assistance of FREDERICK A. GODLEY

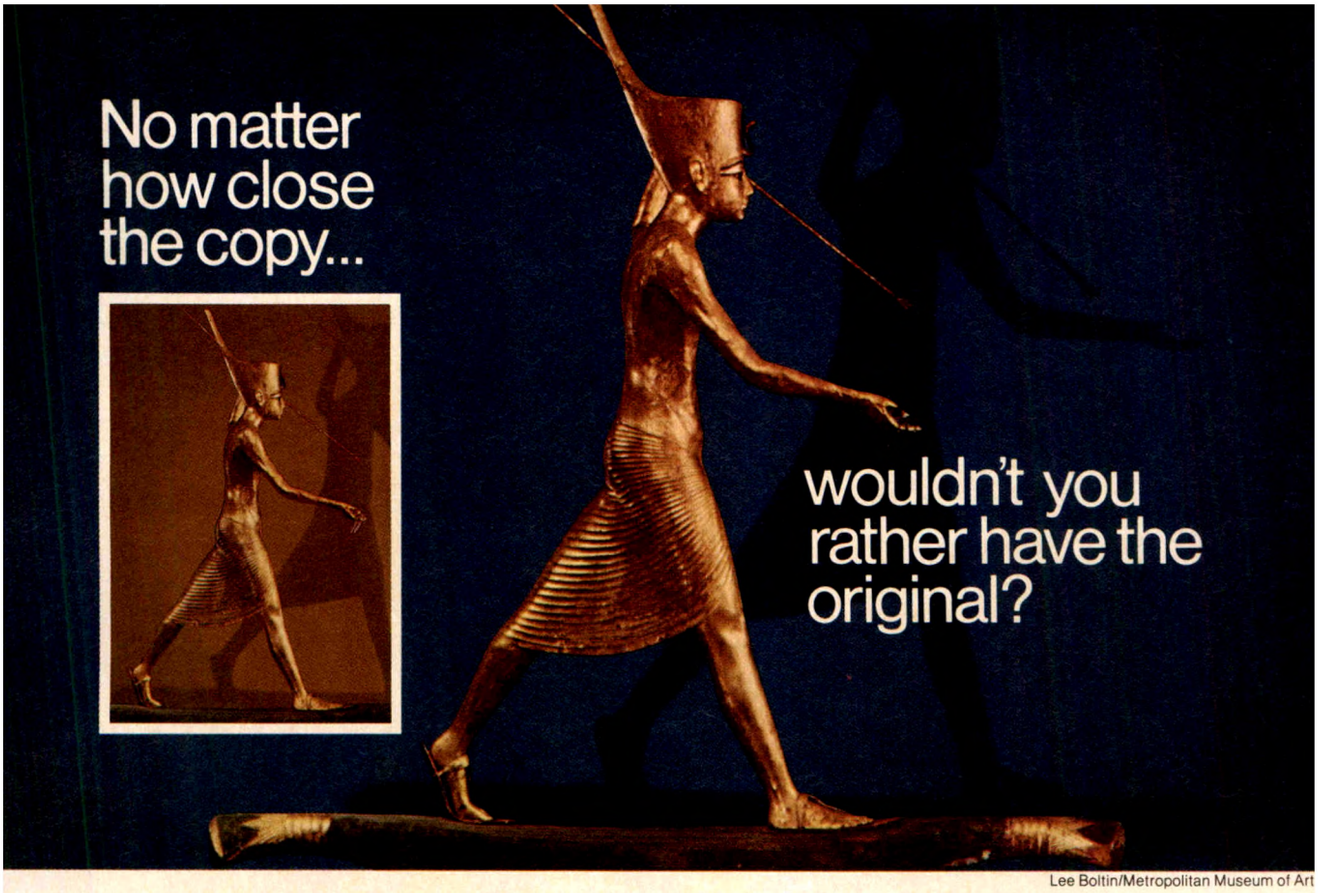
Animal and human studies on the pulmonary uptake of thallium-201 suggest that the increased pulmonary concentration of this isotope during exercise is a consequence of left ventricular failure. In dogs balloon obstruction of the left atrium (which increased mean left atrial pressure and pulmonary transit time) and the administration of acetylcholine (which prolonged pulmonary transit time only) increased the extraction fraction of thallium-201 by the lungs from the basal value of 0.09 ± 0.009 at rest to 0.19 ± 0.02. Quantitation of lung activity of 86 patients indicated that the increased ratio of initial/final pulmonary thallium-201 activity in 30 patients with multivessel coronary artery disease was due to a transient absolute increase in the thallium-201 concentration immediately after maximal exercise. Increased lung uptake in the initial images of a thallium stress study should alert the observer to an underlying impairment of left ventricular function.

827 Effect of Selective Coronary Arteriography on Left Ventricular Volumes and Ejection Fraction in Man

LAWRENCE STERN, BRIAN G. FIRTH, GREGORY J. DEHMER, STACEY M. JOHNSON, ROY V. MARKHAM, SAMUEL E. LEWIS and L. DAVID HILLIS

Contrast left ventriculography and selective coronary arteriography are associated with complex changes in ventricular function and circulatory hemodynamics. In this study of 30 patients with assorted cardiac diseases selective coronary arteriography consistently increased left ventricular end-diastolic pressure from 13.0 ± 6.5 mm Hg before coronary arteriography to 16.1 ± 7.0 mm Hg immediately after but did not affect left ventricular volumes or ejection fraction, even in those with severely compromised left ventricular function. Intracardiac pressures should therefore be measured before the injection of radiographic contrast material, but left ventricular volumes and ejection fraction can be quantitated at any time during catheterization. It may be preferable to assess coronary arterial anatomy first in patients in clinically unstable condition and then evaluate left ventricular volumes and ejection fraction.

continued on page A32



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INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and /or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS— Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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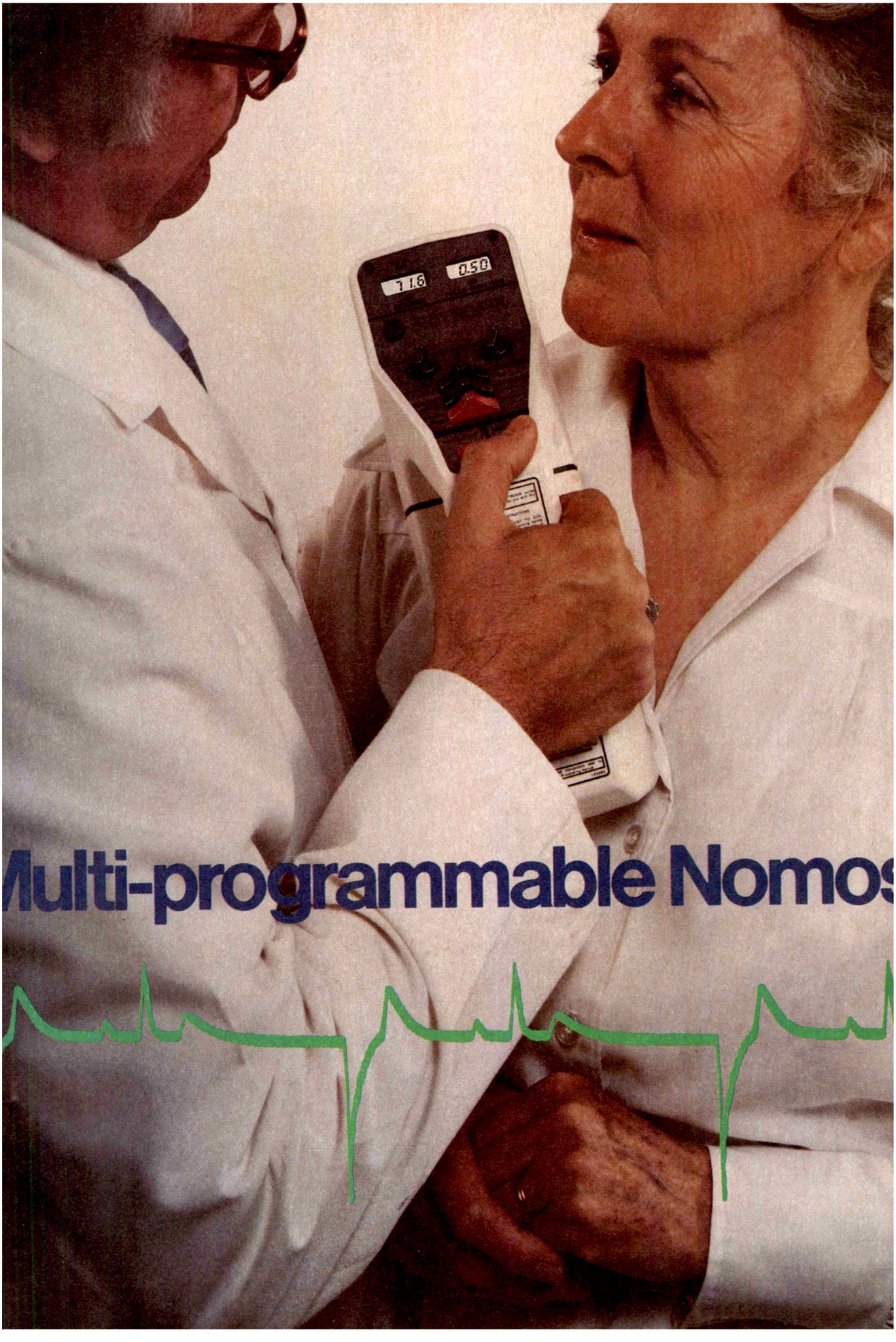
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THE DAWN OF A NEW ERA IN PREVENTIVE MEDICINE

Recently, an official government bulletin indicated that the following professional guideline labeling will be published:

There is evidence that aspirin is safe and effective for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli.

There is no evidence that aspirin is effective in reducing TIA's in women, or is of benefit in the treatment of completed strokes in men or women.

Patients presenting with signs and symptoms of TIA's should have a complete medical and neurologic evaluation.

Consideration should be given to other disorders which resemble TIA's.

It is important to evaluate and treat, if appropriate, other diseases associated with TIA's and stroke, such as hypertension and diabetes.

The recommended dosage for this new indication is 1,300 mg/day (650 mg twice/day or 325 mg four times a day).

Prostaglandin inhibition— the key to aspirin's succes

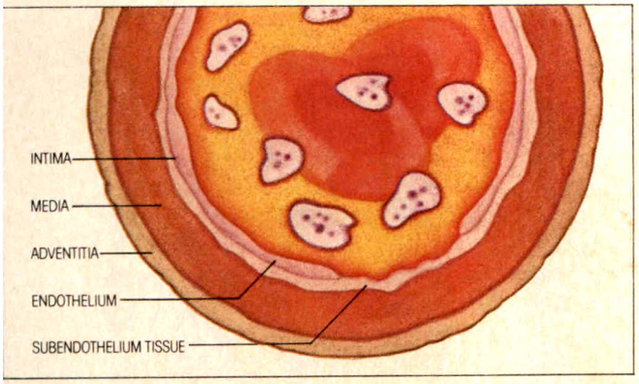
With the ability of aspirin to reduce the risk of recu rent TIA's and stroke clearly demonstrated in tw major multicenter studies,[1,2] physicians throughou the country can now provide their own TIA patien with the prophylactic benefits of Bayer Aspirin.

At the same time, important new research being conducted to determine the full scope aspirin benefits in vascular disease...and in mar other disorders involving prostaglandin synthesis

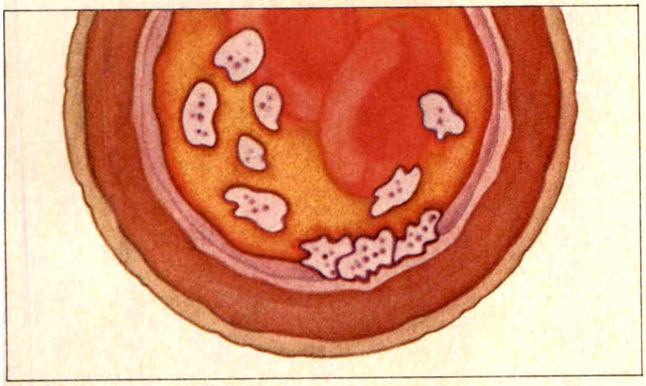
It has become apparent that many of aspirir therapeutic effects—including its analgesic, an pyretic, anti-inflammatory and antithrombot actions, can be traced entirely, or in part, to i ability to inhibit prostaglandin formation.

Prostaglandins are produced by every orga in the body with far reaching effects.[3] In vascula disease, for example, it is the excess productic of the prostaglandin derivative, thromboxane A that can ultimately lead to embolus formation.

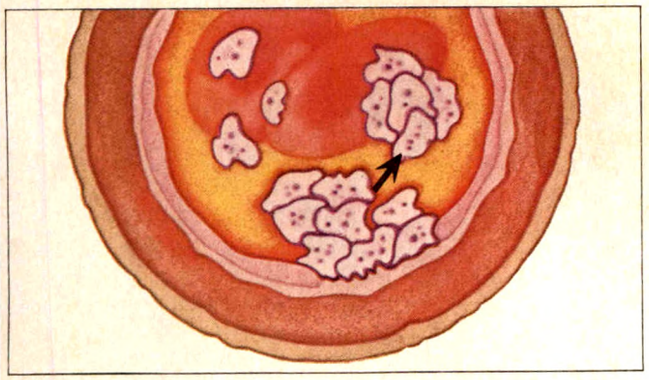
Cross-section of artery—artist's interpretation of circulating platelets encountering area of erosion in arterial wall.



Cerebrovascular clot formation begins when platelets circulating in the blood encounter an area of vascular erosion (usually predisposed by atherosclerosis)...with its exposed subendothelial tissue and collagen.



Through a series of prostaglandin interactions, a platelet collagen reaction takes place—first provoking platelet adhesion, then stimulating a self-perpetuating process of secretion, and finally, aggregation. Once formed, thrombi may dislodge.



By inhibiting platelet cyclo-oxygenase, an enzyme that mediates prostaglandin formation, aspirin inhibits thromboxane synthesis, prevents adhesion and thrombus formation and precludes thrombus dislodgment and subsequent TIA or stroke.

Bayer Aspirin and continuing investigations

Of the large number of pharmaceutical agents capable of altering platelet function, only aspirin has been shown to produce effects that are irreversible for the life of the platelet.[4]

Thus, the use of aspirin is being intensively investigated in a number of possible new clinical areas in which its antiplatelet, prostaglandin-inhibiting effects may be beneficial.

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The Bayer Company is pleased not only to lend its continuing support to wide-ranging investigational studies, but to provide the medical community with comprehensive services and materials concerning aspirin.

The ability to reduce the risk of TIA or stroke with a drug as widely accepted, well tolerated and inexpensive as Bayer Aspirin, certainly represents the dawn of a new era in preventive medicine.

1. Fields, W.S. *et al.*: Stroke *8*:301 (May/June) 1977.
2. The Canadian Cooperative Study Group: N. Engl. J. Med. *229*:54 (July 13) 1978.
3. Robinson, D.W.: Resident & Staff Phys: *25*:92 (Feb) 1979.
4. Fields, W.S. Drugs *18*:150, 1979.

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832 Semiautomated Method for Evaluation of Left Ventricular Regional Wall Motion in Coronary Artery Disease

SANFORD E. WARREN, VALMIK BHARGAVA, WALTER V. R. VIEWEG, GEORGE W. DENNISH, JOSEPH S. ALPERT and ARTHUR D. HAGAN

This correlation of subjective visual inspection of regional left ventricular wall motion with objective computer-determined percent change in the square root of the area between systolic and diastolic outlines in 436 ventriculograms suggests that the latter technique is valuable as both a check on subjective ventriculographic readings and a permanent quantitative document. This study was not designed to and does not resolve whether the computer or the subjective technique is more correct, but it examines objective regional wall motion analysis in the light of current practice (subjective analysis).

837 High Speed Rotating Scanner for Transesophageal Cross-Sectional Echocardiography

KOHZOH HISANAGA, ASAKO HISANAGA, NORIO HIBI, KINYA NISHIMURA and TADASHI KAMBE

Use of a newly developed transesophageal ultrasonic rotating scanner that rotates a single transducer through a full 360° in the esophagus at a rate of 15 to 50 cycles produced high quality images of most portions of the heart with no serious complications and only slight gagging. This system provides a wider area for study of the heart than is available with a conventional external system. Future applications include the detection of left atrial thrombus, demonstration of a much larger area of both ventricles than is obtained with external views, and easier analysis of right and left ventricular anterior wall motion and of valve diseases and disorders. As yet, this method is difficult to perform in infants or children without sedation.

PEDIATRIC CARDIOLOGY

843 Prognostic Significance of Arrhythmia in Tetralogy of Fallot After Intracardiac Repair

HANS U. WESSEL, CHRISTIAN K. BASTANIER, MILTON H. PAUL, TERESA E. BERRY, ROGER B. COLE and ALEXANDER J. MUSTER

This study of the significance of arrhythmia and conduction defects in 395 patients subjected to intracardiac repair of tetralogy of Fallot between 1958 and 1976 shows no tachyarrhythmias, less first degree atrioventricular block and more complete right bundle branch block in patients more recently operated on. The overall incidence of arrhythmia events on routine electrocardiography was 19 percent. There was not a large incidence of severe ventricular arrhythmia when ventricular ectopic rhythm was present at rest. In the majority of these patients ventricular arrhythmia was suppressed when the sinus rate approached or exceeded the rate of the ectopic pacemaker during exercise. Exercise induced no tachyarrhythmia. Arrhythmias were least common in patients with primary intracardiac repair and more common in those with palliation before intracardiac repair or with multiple intracardiac repairs. Patients with arrhythmia or bifascicular block usually had a benign course without strong evidence of arrhythmia progression.

849 Pulsed Doppler Echocardiographic Evaluation of the Cyanotic Newborn: Identification of the Pulmonary Artery in Transposition of the Great Arteries

JAMES GEOFFREY STEVENSON, ISAMU KAWABORI and WARREN G. GUNTHEROTH

In a series of 68 cyanotic neonates with two ventricles and two great vessels, pulsed Doppler echocardiography established that ductal patency is prevalent in the cyanotic neonates, that detection of ductal flow can define the pulmonary artery and that such definition helps resolve the question of transposition of the great arteries in infants with a relation of the great vessels that is neither normal nor suggestive of transposition. On M mode examination the relations of the great vessels were normal in 43 infants; pulsed Doppler echocardiography detected a patent ductus arteriosus flowing into a normally positioned pulmonary artery in all. The cyanosis in all 43 was later proved to be of pulmonary origin. Pulsed Doppler echocardiography equipment is less expensive. The method provides physiologic input into the great vessel diagnosis by identifying the pulmonary artery and screening for severe pulmonary hypertension and intracardiac defects that may not be detectable by other noninvasive means. It reduces the need for cyanotic neonates to undergo cardiac catheterization.

continued on page A38



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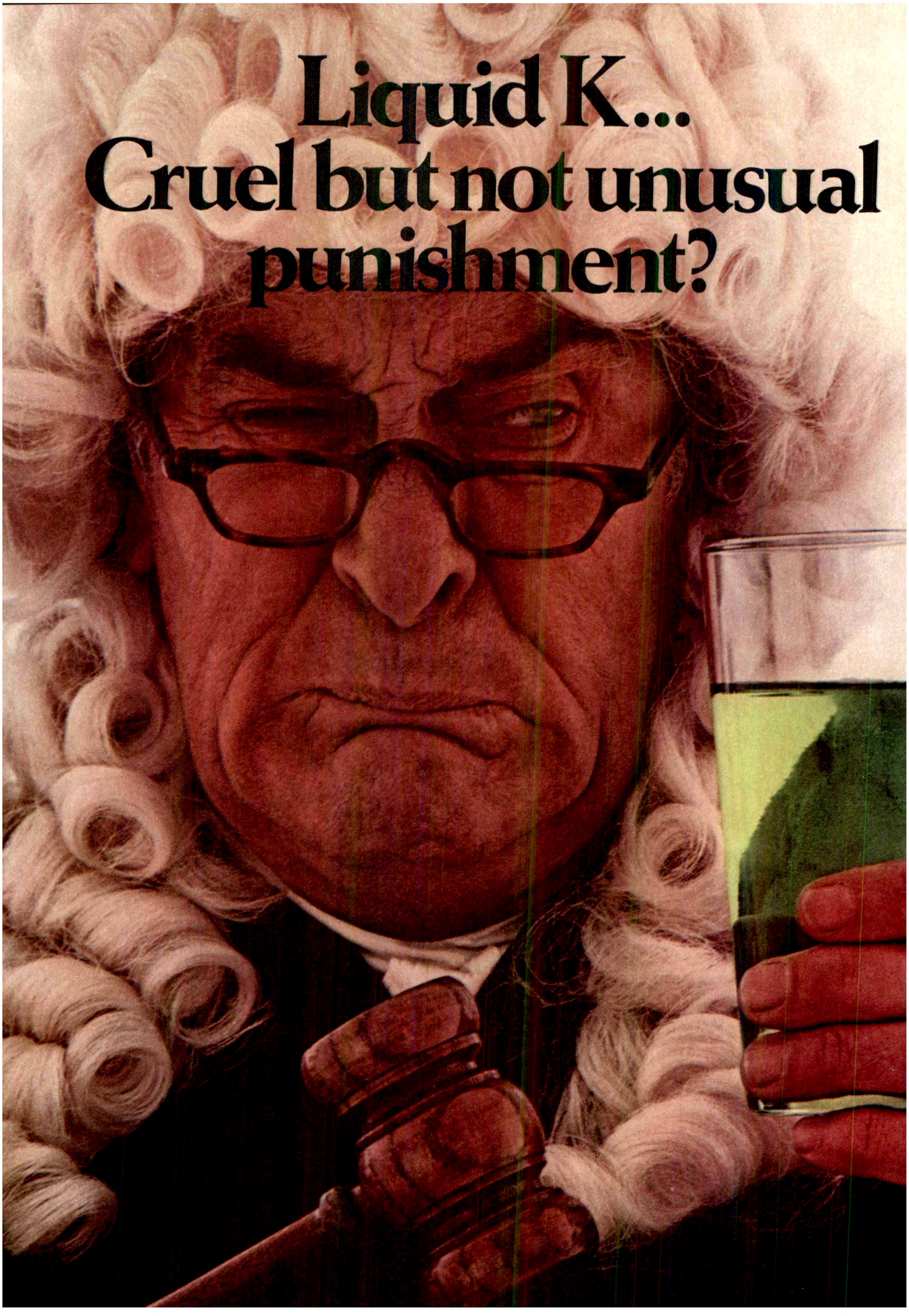
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The cost of a day's therapy with Slow-K is minimal. With its excellent record of efficacy, safety, and patient acceptability, Slow-K is number one at any price.

*Slow-release potassium chloride tablets should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid K preparations because of reports of GI ulceration and bleeding with slow-release KCl tablets (total number of GI lesions in both foreign countries and the United States remains less than one per 100,000 patient-years). The incidence of lesions with enteric-coated KCl tablets is 40-50 per 100.000 patient-years.

References

1. Gunnells JC, Orgain ES, McGuffin WL. Treatment of systemic hypertension, in *The Heart* (ed. 4), Hurst JW, Logue RB, Schlant RC, Wenger NK (Eds.), New York, McGraw-Hill Book Company, 1978, p 1439.
2. Tarpley EL. Controlled-release potassium supplementation. *Curr Ther Res* 1974 (July); **16**(7):734-741.
3. Data on file, CIBA Pharmaceutical Company.

Please turn page for brief prescribing information.

Used in over 4 million patients in the U.S. alone[3]... Slow-K



C I B A

SLOW-K®
potassium chloride slow-release tablets

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings): other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

667112 C78-23 (4/78)

Consult complete product literature before prescribing. 128-2723-A

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA

Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

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REPORTS ON THERAPY

855 Efficacy, Plasma Concentrations and Adverse Effects of A New Sustained Release Procainamide Preparation

ELSA-GRACE V. GIARDINA, PAUL E. FENSTER, J. THOMAS BIGGER, Jr., MICHAEL MAYERSOHN, DONALD PERRIER and FRANK I. MARCUS

Sustained release procainamide proved an effective antiarrhythmic agent as indicated by the greater than 90 percent suppression of ventricular premature depolarizations in 76 percent of 33 patients with this arrhythmia. This agent was also potent against complex forms of ventricular arrhythmias, including paired complexes, ventricular tachycardia and ventricular premature depolarizations with the R on T phenomenon. Adverse drug effects, which appeared early in 52 percent of the group, were minor and abated within 24 hours after administration of the drug was stopped. There was a relation between high procainamide and N-acetylprocainamide plasma concentrations and untoward drug effects. The steady plasma drug concentrations attained with the new formulation allow a longer dosing interval, which is a significant improvement over that of the conventional procainamide preparation.

863 Further Insights Into Digoxin-Quinidine Interaction: Lack of Correlation Between Serum Digoxin Concentration and Inotropic State of the Heart

PAUL D. HIRSH, HOWARD J. WEINER and ROBERT L. NORTH

The results of this digoxin-quinidine interaction study in nine healthy human subjects aged 26 to 31 years support the theory that quinidine displaces digoxin from tissue-binding sites and, more specifically, from cardiac-binding sites. A significant increase of 21 percent was observed in serum digoxin concentrations within 1 to 6 hours after a single oral quinidine dose administered 10 hours after the last digoxin dose. After four doses of quinidine were given over 24 hours, the serum digoxin concentration increased by 59 percent. Further research is needed to determine if this increase in serum digoxin concentration resulting from the digoxin-quinidine interaction is associated with an increased or decreased risk of digitalis toxicity and if the recommendation to reduce the maintenance digoxin dose when concomitant quinidine therapy is initiated is valid.

DIAGNOSTIC SHELF

869 Differentiation of Left Ventricular Pseudoaneurysm From True Aneurysm With Two Dimensional Echocardiography

ROBERT P. GATEWOOD, Jr. and NAVIN C. NANDA

This preliminary study indicates that real time two dimensional echocardiography is a useful and safe noninvasive method for differentiating a pseudoaneurysm from true aneurysm of the left ventricle. Pseudoaneurysm produces a bounded echo-free space with a narrow neck that communicates with the left ventricular cavity. The maximal internal width of this neck (O_{max}) of the aneurysmal sac is much smaller than the maximal parallel internal diameter (D_{max}); the ratio O_{max}/D_{max} never exceeded 0.5. In the true aneurysm the maximal internal width of the mouth (O_{max}) was nearly equal to or actually represented the maximal internal diameter (D_{max}); the ratio O_{max}/D_{max} ranged from 0.9 to 1.0.

879 Gallium-67 Citrate Scanning for Noninvasive Detection of Inflammation in Pericardial Diseases

JOHN B. O'CONNELL, JOHN A. ROBINSON, ROBERT E. HENKIN and ROLF M. GUNNAR

Therapy for acute nonspecific pericarditis not complicated by constriction or impending tamponade is controversial. The development of a noninvasive reproducible technique for detecting and assessing a pericardial inflammatory reaction is necessary before properly controlled clinical studies testing the efficacy of corticosteroids versus nonsteroid agents in nonbacterial pericardial inflammation can be completely interpreted. Data in four patients with acute pericarditis indicate that the inflammation-avid isotope, gallium-67 citrate, which localized in the cardiac silhouette of all, may provide the marker of inflammation and its resolution necessary for the success of such therapeutic studies.

continued on page A43

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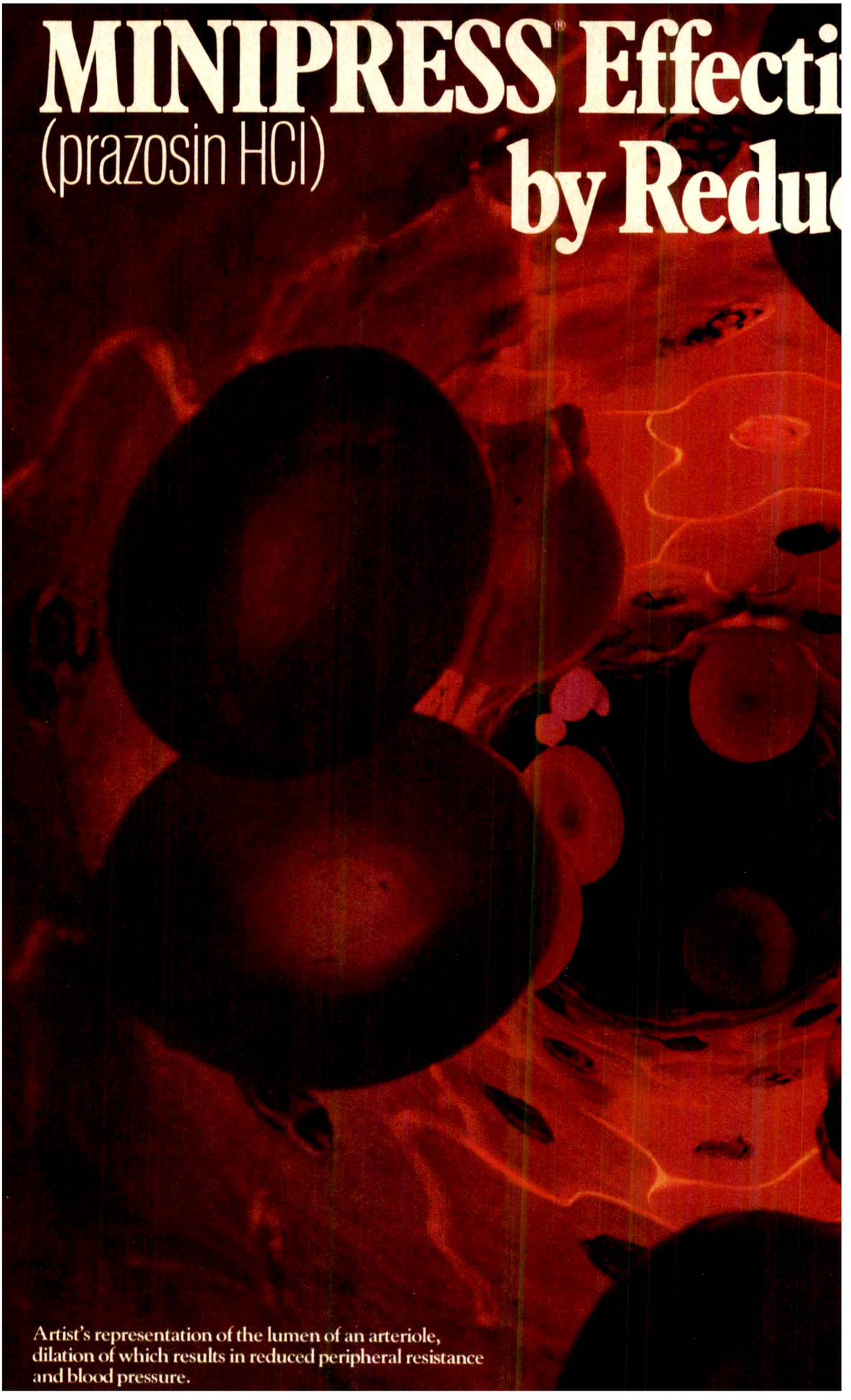
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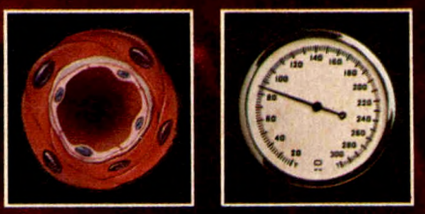
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Controls Hypertension
Peripheral Resistance



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...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

■ Rest ■ Exercise

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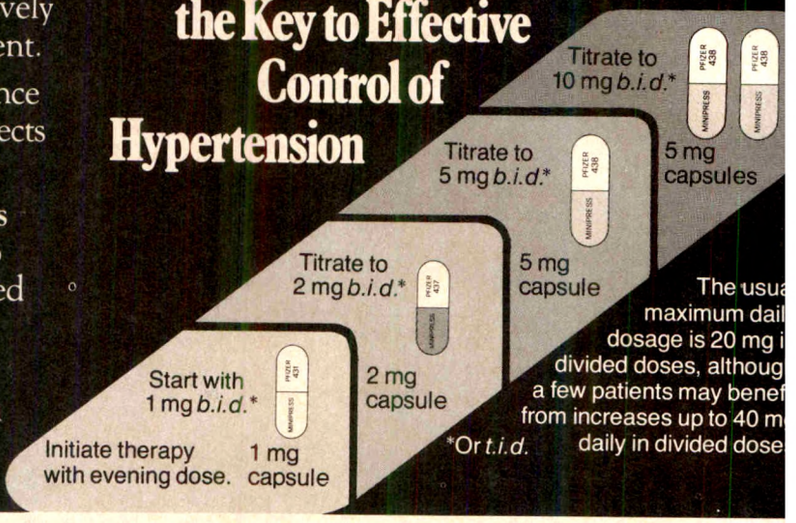
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

Please see Brief Summary on last page.

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- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.



BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

Pfizer **LABORATORIES DIVISION**
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CASE REPORTS

885 Congenital Hypoplasia of Portions of Both Right and Left Ventricular Myocardial Walls. Clinical and Necropsy Observations in Two Patients With Parchment Heart Syndrome

BRUCE F. WALLER, ELDON R. SMITH, BRIAN D. BLACKBOURNE, FELIX P. ARCE, NELLIE N. SARKAR and WILLIAM C. ROBERTS

Clinical and morphologic data in 2 patients with congenital hypoplasia of portions of both right and left ventricular free walls in the absence of associated coronary or valvular heart disease and from 22 necropsy patients in a review of the pertinent literature are presented. Nearly half of these patients died of congestive heart failure in the 1st year of life and the other half reached adulthood with or without manifestations of cardiac dysfunction. The differential diagnosis of congenital hypoplasia of the right ventricular myocardium includes Ebstein's anomaly of the tricuspid valve, idiopathic dilated cardiomyopathy and pulmonary or tricuspid valve atresia. The echocardiogram is useful in distinguishing congenital hypoplasia of the right ventricular myocardium from Ebstein's anomaly by the presence of a dilated right ventricular cavity, delayed tricuspid valve closure, and diastolic opening of the pulmonary valve.

892 Biventricular Hypoplasia With Myocardial Fiber Hypertrophy and Disarray

WILLIAM C. LITTLE, H. CECIL COGHLAN and JACK C. GEER

Postmortem examination of this 25 year old woman with effort intolerance and systemic venous congestion since childhood confirmed an unusual case of cardiac biventricular hypoplasia and dysplasia with fiber hypertrophy and disarray that resulted in restrictive ventricular dysfunction, impaired cardiac output, atrioventricular valve incompetence and marked enlargement of the atria. This condition differs from Uhl's anomaly in that this patient's right ventricle, although quite thin in some areas, contained functioning myocardium and did contract. The patient died after valve replacement surgery.

SPECIAL DEPARTMENTS

897 Letters to the Editor

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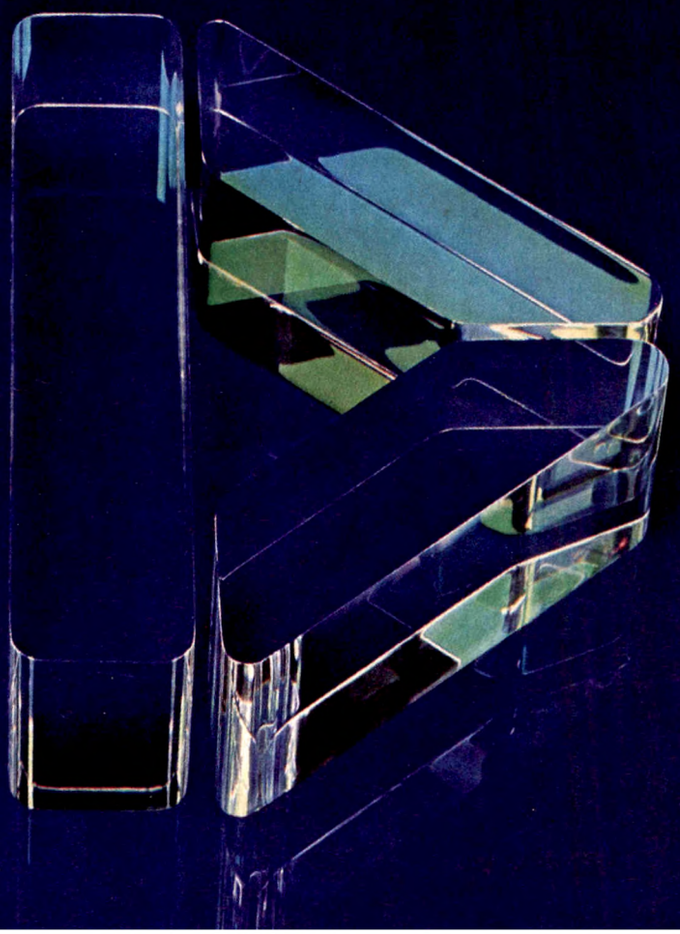
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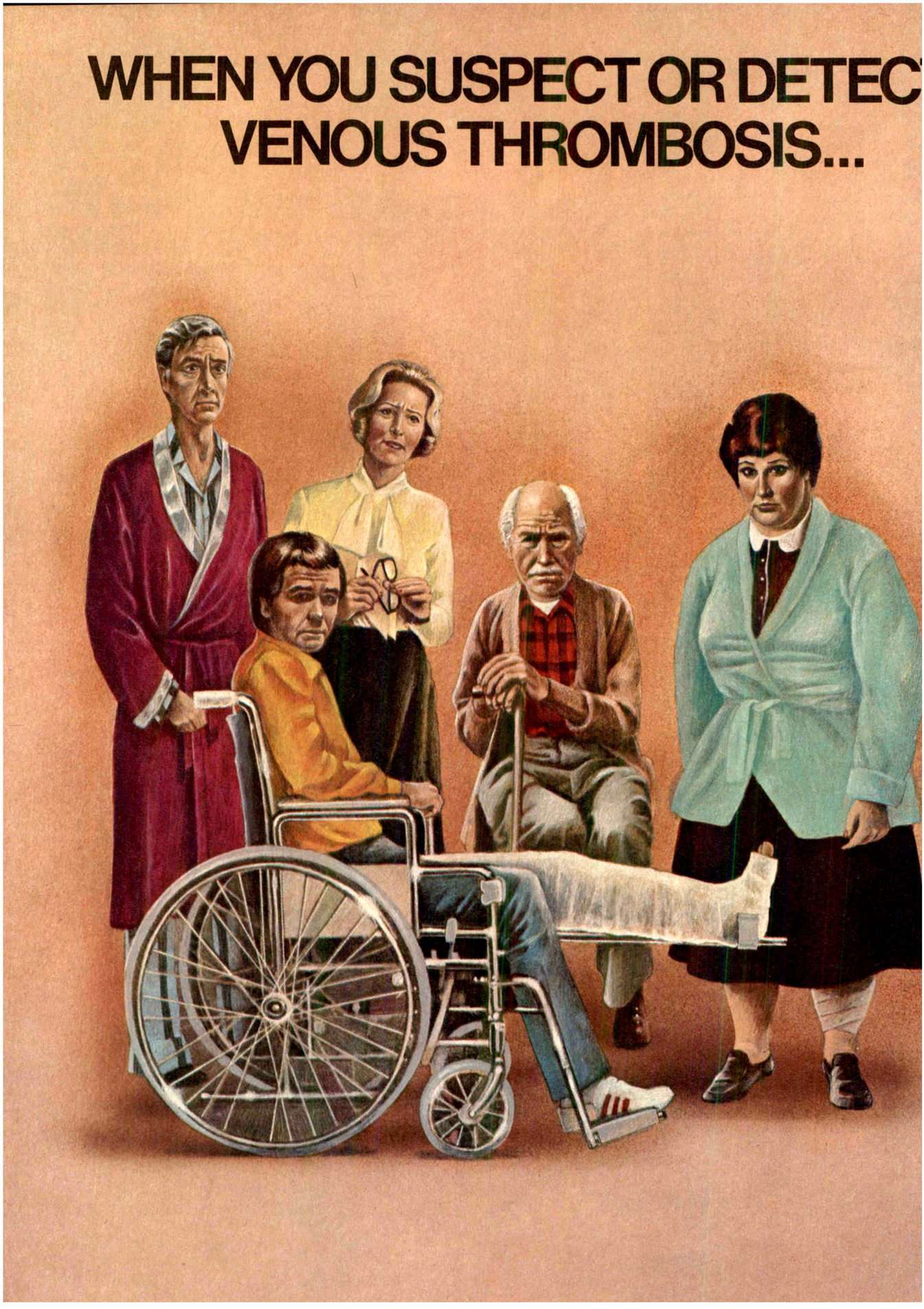


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Thromboembolism: a high risk among patients with one or more of these factors...

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Fractures of lower limb
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Previous venous thromboembolism
Congestive cardiac failure
Cancer surgery
Obesity
Varicose vein surgery

Incidence of venous thrombosis or abnormal scans as shown by ^{125}I-fibrinogen screening in selected high-risk medical-surgical patients

Category	Incidence
Elective surgery	
Major abdominal thoracic/gynecologic	11-65%[1,2]
Retropubic prostatectomy	28-50%[1,2]
Transurethral prostatectomy	4%[1,2]
Emergency surgery	
Hip fracture	48-74%[1,2]
Childbirth	3%[1,2]
Medical	
Myocardial infarction	23-38%[1,2]
Stroke	60%[1]

ORAL ANTICOAGULATION:
Often indicated to lower the risk of thromboembolic complications.

References: 1. Hirsh J, Gallus AS. ^{125}I-labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. *JAMA* 233:970-973, 1975. **2.** Kakkar VV. The diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. *Arch Surg* 104:152-159, 1972. **3.** Ebert RV. Use of anticoagulants in acute myocardial infarction. *Circulation* 45:903-910, Apr 1972. **4.** Borden CW. The current status of therapy with anticoagulants. *Med Clin North Am* 56:235-251, Jan 1972. **5.** Hirsh J, Gallus AS. Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. *Postgrad Med* 55:211-217, Jan 1974.

*For selected patients who have had a large infarct, a history of previous infarction or angina, severe hypotension or shock, chronic atrial fibrillation, congestive heart failure, past history of venous thrombosis or embolism or complications requiring a prolonged period in bed.

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Effective treatment of atrial fibrillation with embolization
Effective adjunctive treatment of coronary occlusion

Initiation of therapy

Induction – 40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response.

- dosage must be individualized according to patient's prothrombin time
- frequent laboratory monitoring is recommended
- determine prothrombin time daily until results fall within the therapeutic range – 1.5 to 2.5 times normal
- afterwards, prothrombin time must be determined periodically to monitor the patient's course

Maintenance of anticoagulation

- 2-10 mg, for most patients (scored tablets allow flexibility and accurate titration)
- dose and interval should be adjusted according to the individual patient's prothrombin time response

Duration of anticoagulation

- should be individualized for each patient
- in general, should be continued until danger of thrombosis and embolism has passed

Recommendations of prominent clinicians on duration of therapy

in myocardial infarction[3,4*]	1-3 years* (reevaluate at least every 6 months)
in pulmonary embolism[4,5]	6 weeks-6 months
in deep vein thrombosis[4,5]	6 weeks-6 months

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crystalline warfarin sodium, U.S.P.*

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts, (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; (4)pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

*Present as crystalline sodium warfarin isopropanol clathrate.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X are not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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INDICATIONS:
1. **Congestive heart failure:** Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. **Atrial fibrillation:** Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. **Atrial flutter:** Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. **Paroxysmal atrial tachycardia:** Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. **Cardiogenic shock:** The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:
Gynecomastia: Uncommon.

Overdose or toxic effects in adults:
Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:
Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Calcific Deposits in Porcine Bioprostheses: Structure and Pathogenesis

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Gross, histologic and ultrastructural studies were made of 14 porcine valve bioprostheses that were found to contain calcific deposits at the time of removal either at reoperation (13 patients) or at necropsy (1 patient). Eleven bioprostheses had been in the mitral position, 1 in the aortic, 1 in the tricuspid and 1 in a pulmonary conduit. The ages of the patients at the time of implantation ranged from 2.5 to 65 years (average 32), and the bioprostheses had been in place from 3 to 94 months (average 39). Analysis of these 14 bioprostheses and review of reports concerning 37 other calcified porcine bioprostheses suggest the following conclusions: (1) Calcific deposits occur commonly in bioprostheses implanted in patients of all ages, but are more likely to become severe and clinically significant in children and in young adults than in older patients. (2) Calcific deposits can lead to prosthetic valve stenosis, because they can limit the mobility of the cusps; however, they can also be associated with prosthetic valve regurgitation. (3) Metabolic disorders that could contribute to bioprosthetic calcification are not identifiable in most patients having calcified prosthetic tissue valves. (4) The two main sites of deposition of calcium phosphate in porcine valve bioprostheses are the connective tissue in the cusps, particularly in the spongiosa, and small thrombi on the surfaces. (5) Calcification of connective tissue first involves the collagen fibrils; calcification of thrombi involves the mitochondria in platelets and leukocytes trapped in the mesh of fibrin. From these two sites, calcific deposits can grow and spread into other areas of the cusps.

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A large majority of patients undergoing cardiac valve replacement with glutaraldehyde-treated porcine bioprostheses follow a clinically satisfactory course for the first 5 years after operation. Nevertheless, clinical and morphologic studies have documented certain complications leading to malfunction of porcine bioprostheses, mainly cuspal infection, perforation and calcification. Previous reports from our laboratory[1–3] have described gross, histologic and ultrastructural alterations developing in perforated or infected porcine bioprostheses. Calcification of porcine bioprostheses received little attention until recently, when isolated case reports[4–20] emphasized its occurrence, particularly in children and young adults. Although this complication may lead to a reduction in the mo-

bility of the cusps and to bioprosthetic stenosis or regurgitation, detailed studies have not been made of the precise location, structure and pathogenesis of calcific deposits in porcine bioprostheses. This study presents morphologic observations on 14 porcine bioprostheses that were found to contain calcific deposits when removed after being in place from 3 to 94 months.

Methods

Patients (Table I)

The 14 patients had calcific deposits in the cusps of the porcine bioprostheses manifested on either gross or microscopic examination. Seven patients had been included in previous clinical reports.[1,2,16,19,21,22] The patients, six boys or men and eight girls or women, ranged in age from 2.5 to 65 years (mean 32) at the time of bioprosthetic implantation.

Six patients had rheumatic heart disease, six had congenital heart disease, one had infective endocarditis and one had pure mitral regurgitation of uncertain origin. Twelve patients underwent single valve replacement by a porcine bioprosthesis: nine had mitral valve replacement, one aortic valve replacement, one tricuspid valve replacement and one pulmonary valve replacement. The tricuspid valve was replaced in one patient with transposition of the great vessels; thus, it functioned as a systemic atrioventricular valve and hereafter will be considered as a "mitral" replacement. The pulmonary valve was replaced by a Hancock conduit in a patient with pulmonary valve atresia and ventricular septal defect. Two patients underwent replacement of both the mitral and the tricuspid valve: Patient 13 had severe stenosis of both natural valves; both implanted porcine bioprostheses eventually became regurgitant and had to be replaced; however, only the bioprosthesis in the tricuspid position became calcified. Therefore, the mitral bioprosthesis in this patient is not included in the study. Patient 8 had pure mitral and tricuspid regurgitation resulting from infective endocarditis; after double valve replacement, a new episode of infective endocarditis developed and the porcine bioprosthesis in the mitral position was removed. The bioprosthesis in the tricuspid position did not become infected and was not removed at reoperation.[1] The bioprosthesis in Patient 14, who died of mitral regurgitation of the bioprosthesis 94 months after its implantation, was recovered at necropsy. The 13 other bioprostheses were recovered at reoperation. The time interval between implantation and operative removal of the bioprostheses ranged from 3 to 94 months (average 39).

In 8 of the 13 patients who underwent reoperation, the procedure was performed because of prosthetic valve stenosis occurring 10 to 60 months (average 34) after implantation. Six of the eight stenosed bioprostheses had been placed in the mitral position, one in the aortic position and one in a pulmonary conduit. Another patient underwent reoperation because of a perivalvular leak 3 months after implantation; the bioprosthesis showed only minimal (clinically insignificant) calcific deposits. Three additional patients underwent reoperation because of prosthetic valve regurgitation caused by cuspal perforation or dehiscence. Patient 8 underwent reoperation because of prosthetic mitral infection causing both stenosis and regurgitation.

Examination after removal disclosed cuspal perforations in six bioprostheses that had been implanted for periods of 18 to 94 months (average 52). One patient had chronic renal insufficiency attributed to cephalothin toxicity; other metabolic diseases were not identified in any of the other patients.

Procedures

After removal, the bioprostheses were fixed with cold, 3 percent glutaraldehyde in 0.1 *M* phosphate buffer, pH 7.2, and processed for light and electron microscopic study. The bioprostheses were radiographed after fixation. For light microscopic examination, selected portions of the cusps were trimmed, decalcified with a mixture of sodium citrate and formic acid and embedded in paraffin. Histologic sections were stained according to the following methods: hematoxy-

TABLE I

Clinical and Morphologic Findings in 14 Patients With Calcific Deposits in Porcine Bioprostheses

Case	Age (yr) at PB Implantation	Sex	Valve Lesion	Site of PB	PB Size (mm)	PB Removal		PB Cuspal Changes				Previous Clinical Reports of Patients (reference)
						Time (mo)	Cause	Gross Ca^{++}	Perf. Leaf.	Red. Mob.	Thr.	
1	2.5	M	MS (cong)	M	19	41	S	+	0	+	0	Pt. 6[16]
2	3.5	F	TGV-TR	M*	23	37	S	+	0	+	0	
3	5.5	F	MR (cong)	M	. . .	30	S	+	+	+	0	
4	8	F	MR (cong)	M	27	35	R	+	+	+	0	Pt.[22]
5	9	F	MR	M	29	18	S	+	+	+	0	Pt. 5[19]
6	11	M	PVA-VSD	PC	20	60	S	+	0	+	0	
7	23	F	AS	A	. . .	10	S	+	0	0	+	
8	28	M	IE,MV/TV	M	35	4.5	IE	+	0	+	+	Pt. 3[1]
9	42	M	MR	M	35	28	S,R,IE	0	0	0	0	Pt. 4[1]; Pt. 10[2]
10	55	F	MS	M	31	76	R	+	+	0	0	Pt. 12[2]; Pt.[21]
11	61	M	MS	M	29	3	PVL	0	0	0	+	Pt. 7[2]
12	65	F	MS	M	29	48	S	+	0	+	0	
13	65	F	MS,TR,TS	T	33	63	R	0	+	0	0	
14	65	M	MS	M	31	94	Death	+	+	+	0	

* Systemic atrioventricular valve.

A = aortic valve; AS = aortic stenosis; Ca^{++} = calcium; cong = congenital; IE = infective endocarditis; IE,MV/TV = infective endocarditis affecting the mitral and tricuspid valves; M = mitral valve; MR = mitral regurgitation; MS = mitral stenosis; PB = porcine bioprosthesis; PC = pulmonary conduit; Perf. Leaf. = perforated leaflet; Pt. = patient; PVA-VSD = pulmonary valve atresia-ventricular septal defect; PVL = perivalvular leak; R = regurgitation; Red. Mob. = reduced mobility of cusps; S = stenosis; T = tricuspid valve; TGV = transposition of the great vessels; Thr. = thrombus; TR = tricuspid regurgitation; TS = tricuspid stenosis; + = present; 0 = absent; . . . = information not available.

lin-eosin, Masson trichrome, Movat pentachrome, phosphotungstic acid-hematoxylin and von Kossa.

For study by transmission electron microscopy, tissues were processed as previously described.[2] For X-ray energy dispersive microanalysis of the calcific deposits, 1,000 Å thick sections of Maraglas®-embedded tissues were prepared, mounted on beryllium grids and examined with an ETEC scanning electron microscope equipped with an EDAX detector.

Results

Gross anatomic observations (Table I): Calcific deposits were grossly evident in 11 of the 14 recovered bioprostheses, and in 9 of these the flexibility and mobility of the cusps were reduced. In 10 of the 11 bioprostheses (from Patients 1 to 7, 10, 12 and 14) the calcific deposits were localized to the cusps; in the remaining bioprosthesis (from Patient 8), they involved infected vegetations.[1] Of the three bioprostheses without grossly evident calcific deposits (from Patients 9, 11 and 13), one (from Patient 9) was covered by thrombotic material, which was the site of infection and calcification evident only on microscopic examination[1,2]; another (from Patient 11) contained noncalcified thrombus, and the remaining one (from Patient 13) had a perforated cusp. The latter two bioprostheses (from Patients 11 and 13) had microscopic calcific deposits in the cuspal connective tissue. Thus, none of the 14 bioprostheses were normal on gross anatomic study.

Six of the 14 bioprostheses had one or more perforations in the cusps; 5 of these had grossly evident calcific deposits, which often were closely adjacent to the perforations. In each of the 10 bioprostheses with calcific deposits in the cusps, these deposits appeared similar and consisted of pale yellow, discrete, usually flat plaques that were raised and projected above both surfaces of the leaflets (Fig. 1 and 2). Less frequently, they formed irregularly shaped, conical or bulbous excrescences 1 to 2 mm in height. The calcific deposits tended to involve all three cusps to a similar extent. When minimal in amount, calcific deposits tended to be localized to areas of the cusps immediately adjacent to the commissures; when more extensive, they formed multiple foci including the areas of apposition of the cusps. The most extensive deposits involved the entire area of each cusp.

Histologic observations: The histologic appearance of the grossly visible calcific deposits (Fig. 3 and 4) was similar in each of the 10 bioprostheses with calcified cusps. The largest calcific deposits always involved the spongiosa (Fig. 3A) and sometimes they extended into immediately adjacent regions of the fibrosa and the ventricularis. Some small calcific deposits were confined entirely either to the fibrosa (Fig. 3B) or to the ventricularis. However, the large calcific deposits in the spongiosa more frequently displaced the other layers of the bioprosthesis, giving the appearance of raised plaques. These deposits often were multinodular, and adjacent nodules were separated from one another by fibrin deposits or by clear spaces (Fig. 4). Some of the latter spaces contained erythrocytes. Elastic fibers were devoid of calcium. The larger calcific deposits actually formed parts of the surfaces of the cusps, whose layered structure appeared to have been completely lost (by erosion of the superficial layers) in such areas. The basophilia of the calcific deposits in histologic sections stained with hematoxylin-eosin was much more pronounced in peripheral than in central regions (Fig. 3).

Calcific deposits also were recognized by electron microscopic study in: (1) the cardiac muscle shelf at the base of the right coronary cusp; (2) adipose tissue cells in the space between the aortic wall and the base of the cusps (Fig. 5A); (3) the aortic media at the level of, and just above, the base of the cusp (Fig. 5B); (4) organizing thrombi on the cuspal surfaces; and (5) infected vege-

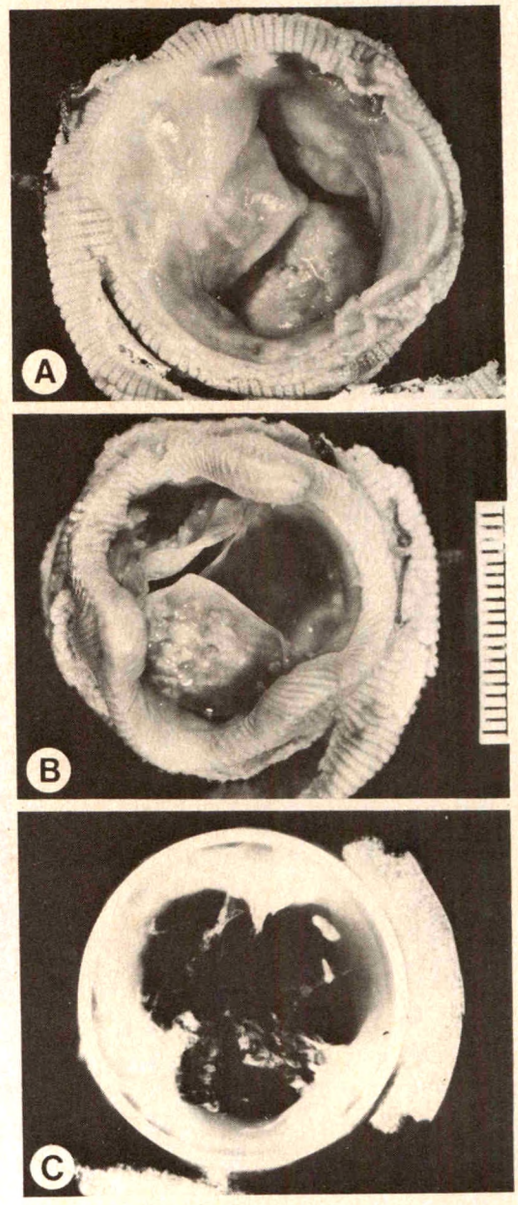


FIGURE 1. Case 12. Photographs of inflow surface (**A**), outflow surface (**B**) and roentgenogram (**C**) of bioprosthesis operatively removed, because of severe stenosis, 48 months after implantation in the mitral position. Calcific deposits are present in each cusp and are prominent in the commissural regions.

tations produced by staphylococci (Patient 8). In the first two of these sites, the calcific deposits were small. However, in the aortic wall the deposits were larger and formed plaques that extended throughout the media. Such deposits, which involved both the smooth muscle cells and the extracellular spaces, had strongly basophilic edges and much less basophilic cores (Fig. 5B). The deposits in the aortic wall were not continuous with those in the cusps, and therefore did not produce bioprosthetic dysfunction. The deposits in young and old patients were similar histologically.

Other histologic changes observed in the biopros theses were (1) separation (delamination) of adjacen layers of connective tissue in the cusps, particularly i the spongiosa, leaving clear spaces that often were fille by proteinaceous material[2]; (2) loss of proteoglyca material from the spongiosa (best demonstrated wit the Movat stain); (3) deposition of mononuclear cell mostly macrophages, and multinucleated giant cells o the surfaces of the cusps, particularly in the outflo surfaces; and (4) focal thinning of the cusps, with frayin and erosion of the connective tissue. In Patients 3 to 5

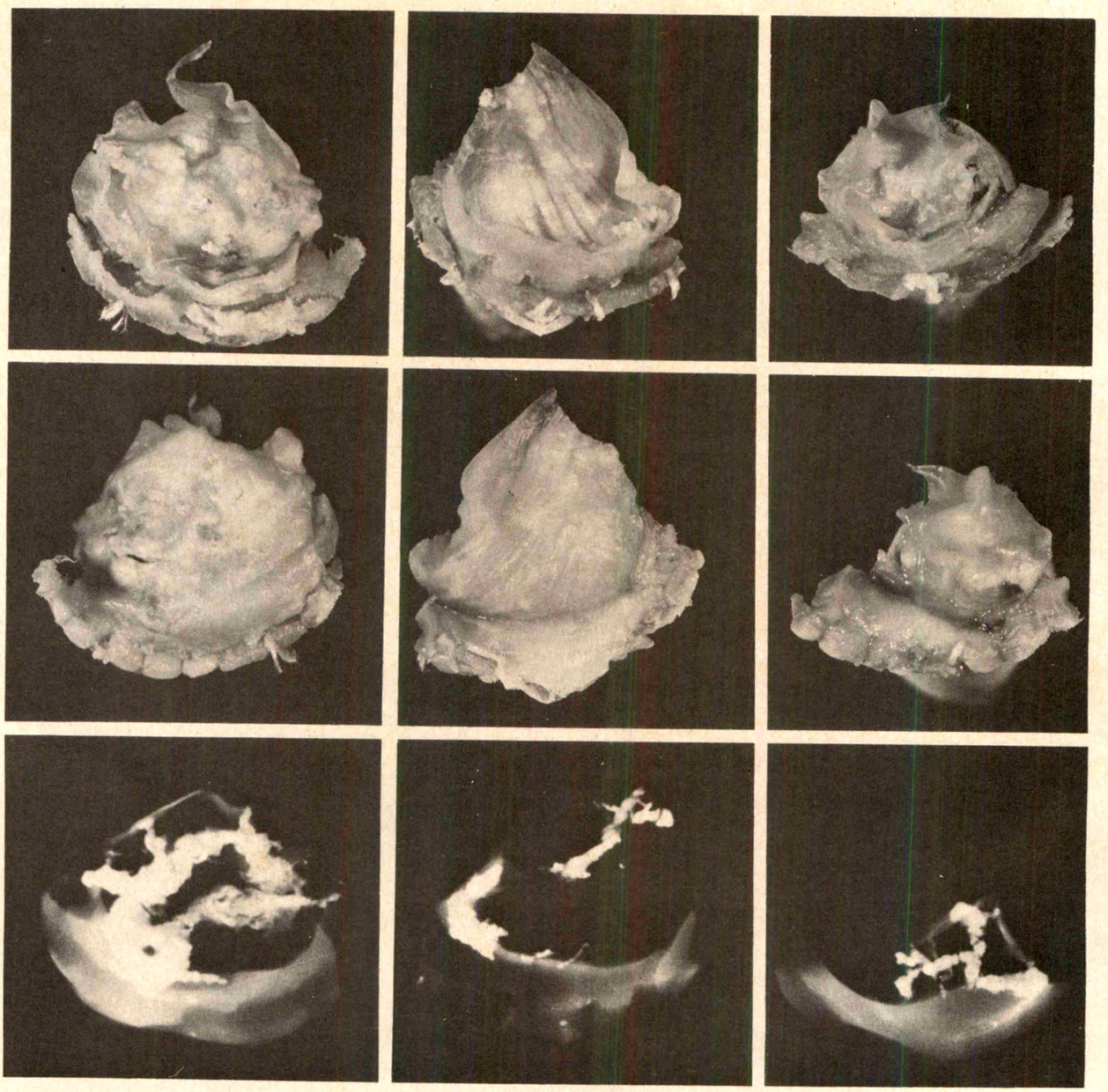


FIGURE 2. Case 1. Outflow surfaces (**top**), inflow surfaces (**middle**) and roentgenograms (**bottom**) of the cusps of bioprosthesis removed at reoperation because of severe stenosis, 41 months after implantation in the mitral position. The true extent of the calcific deposits is difficult to assess from visual inspection, and the roentgenograms show that they consist of streaks that bear no relation to the normal anatomic features of the cusps.

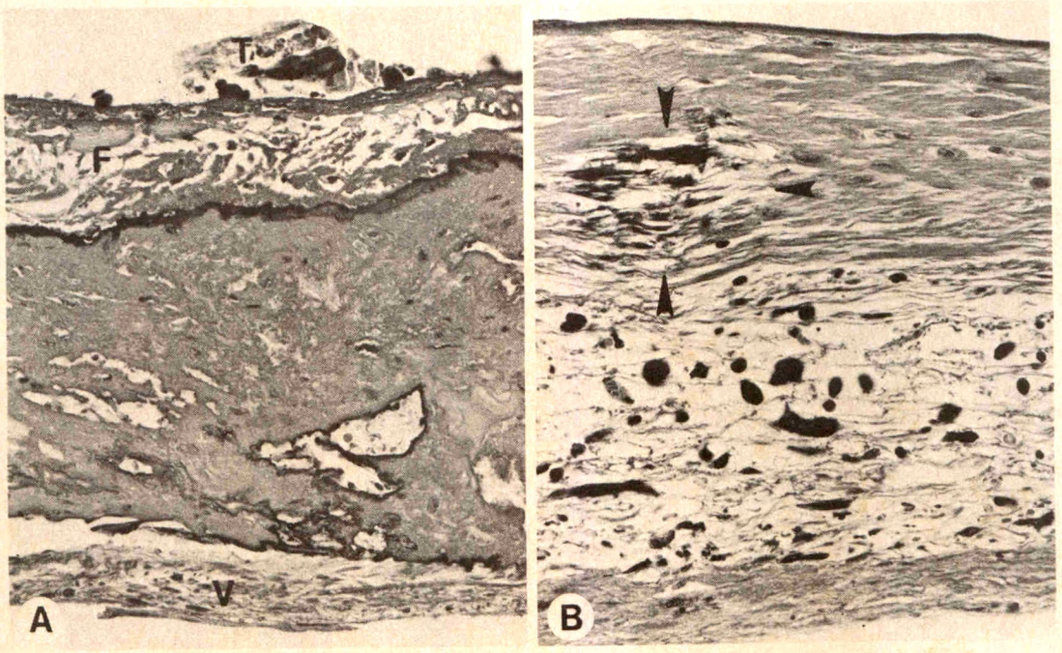


FIGURE 3. Case 3. Light micrographs of calcific deposits in the stenotic bioprosthesis operatively removed 30 months after implantation in the mitral position. **A,** deposit that fills area corresponding to spongiosa of normal cusp. The fibrosa (F) shown at **top** is partially disrupted; a small thrombus (T) is present on the outflow surface, and the ventricularis (V) is shown at **bottom.** Note the dark irregular borders of the calcific deposit and the empty spaces that it still contains (compare with the appearance of the spongiosa in **B. B,** small calcific deposit (**arrowheads**) is localized in fibrosa of bioprosthesis. Note the empty appearance of the spongiosa, which is delaminated and has lost its proteoglycan material. The dark material in the spongiosa probably represents precipitated plasma protein components. The ventricularis appears normal. (Hematoxylin-eosin ×250 [**A**] and Novat pentachrome ×250 [**B**], both reduced by 20 percent.)

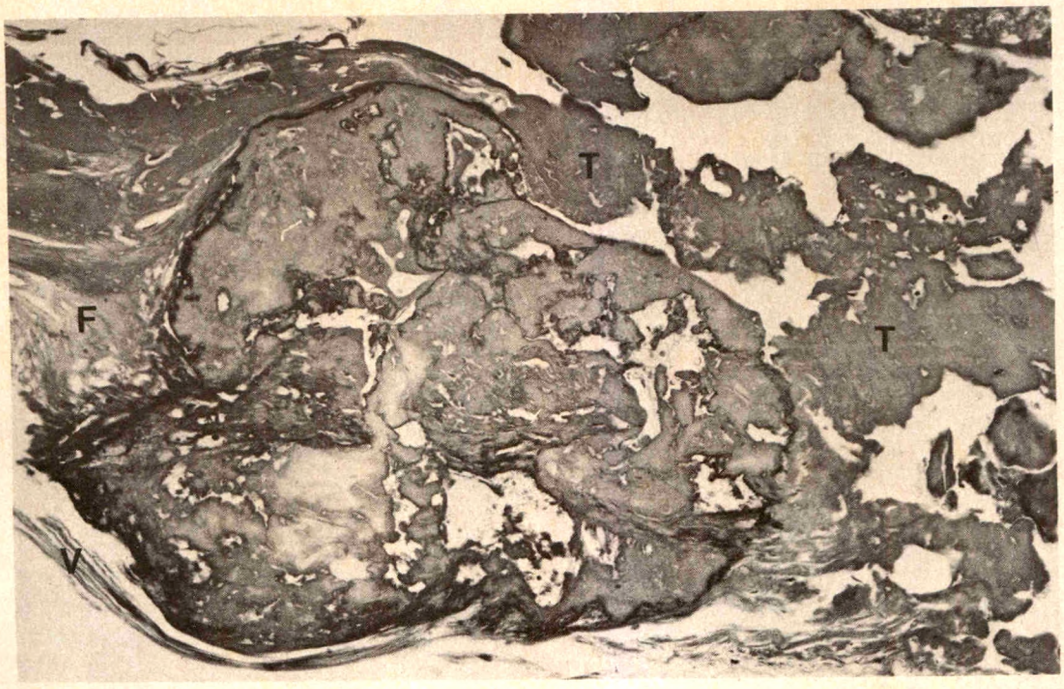


FIGURE 4. Case 3. Histologic appearance of large multinodular calcific deposit occupying practically the entire thickness of the cusp and associated with a large amount of thrombotic material (T), mostly fibrin. The structure of the cusp has been severely altered. Both the fibrosa (F) and the ventricularis (V) appear eroded on the **left** and completely disrupted on the **right.** (Movat pentachrome ×250, reduced by 20 percent.)

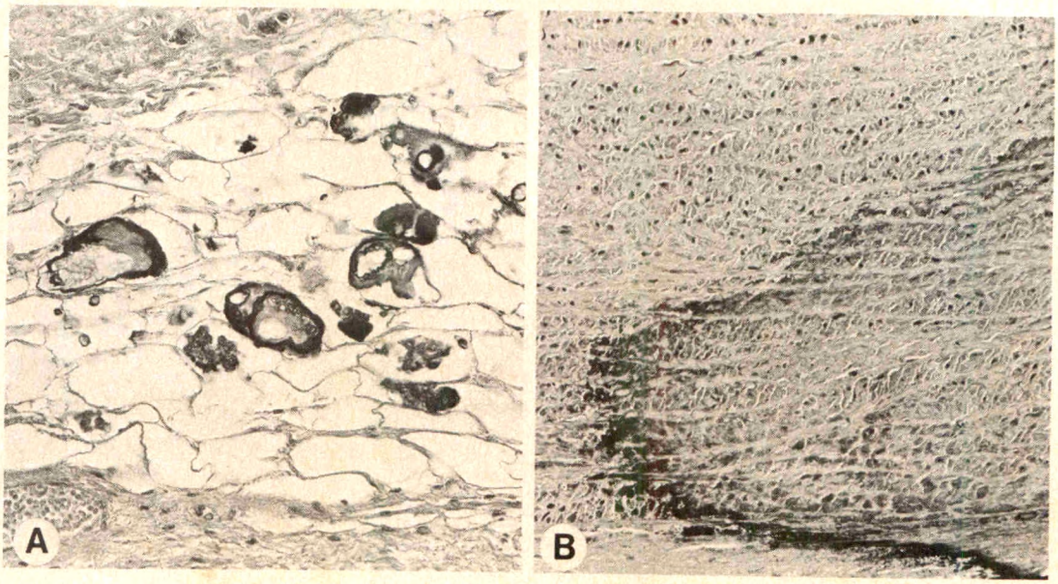


FIGURE 5. Case 8. Calcific deposits in adipose tissue cells at base of cusp (**A**) and in aortic wall (**B**). (Hematoxylin-eosin ×250 and ×150, respectively, reduced by 20 percent.)

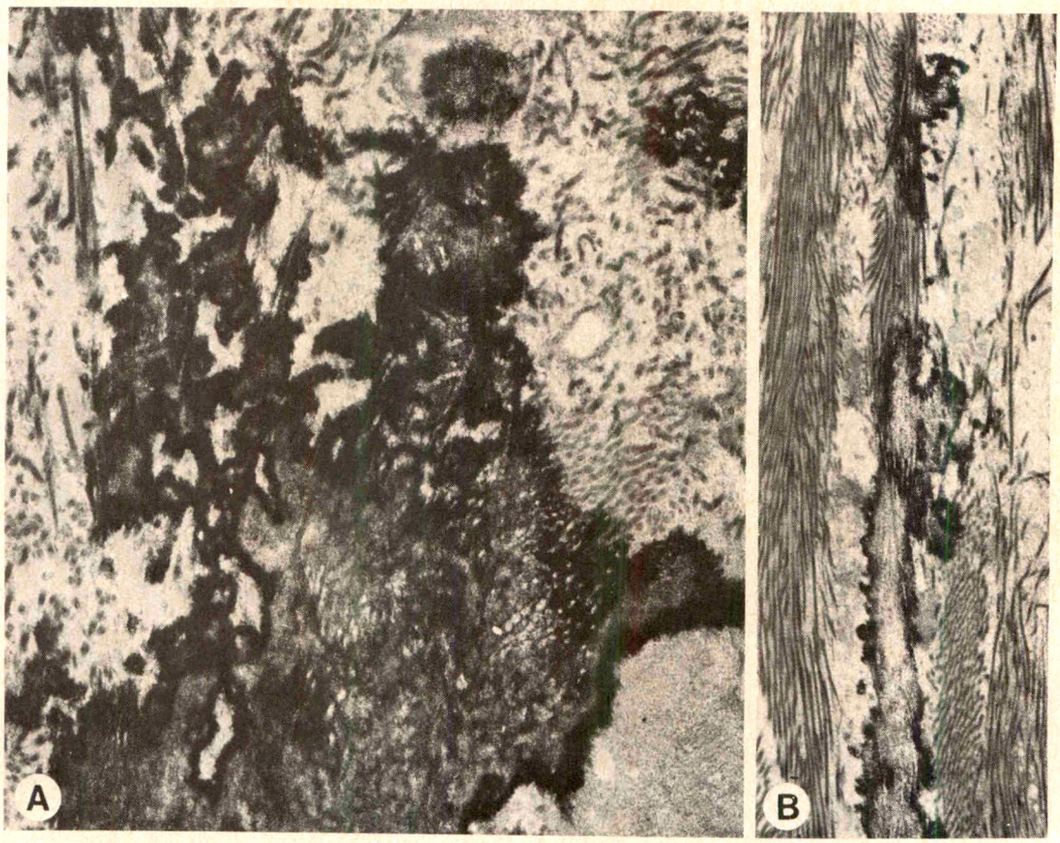


FIGURE 6. Case 3. Electron micrographs of calcific deposits associated with collagen fibrils. **A**, electron-dense crystals of calcium phosphate have completely surrounded several bundles of collagen fibrils at the periphery of a large calcific mass. **B**, small calcific deposit appears to be developing associated with a bundle of collagen fibrils. Note the characteristically dense border of the deposit (×22,000 [**A**] and ×15,000 [**B**], reduced by 20 percent.)

10, 13 and 14, the latter changes were associated with perforation of one or more of the cusps.

Ultrastructural observations: Certain early and late ultrastructural changes in porcine bioprostheses have been described in detail in previous publications from this laboratory.[2,3] Therefore, only changes related to calcification are described herein. Two types of calcific deposits were considered to be of significance in producing bioprosthetic stenosis: deposits related to calcification of cuspal connective tissue structures and deposits related to calcification of surface thrombi.

Calcification of cuspal connective tissue structures consistently involved collagen fibrils (Fig. 6 and 7) but seldom involved cell components of the cusps, and did not involve elastic fibers. Most deposits involved areas in which the collagen fibrils were relatively loosely arranged rather than tightly packed. Calcific deposits associated with collagen fibrils showed three different patterns of organization. In the first of these (Fig. 7, A and B), the calcific deposits directly involved the collagen fibrils but did not extend into the interfibrillary spaces. In the second (Fig. 6, A and B and 7, C and D), the calcific deposits were localized in the periphery of the collagen fibrils and in the interfibrillary spaces; however, the interior of the collagen fibrils was not involved, and the fibrils therefore appeared as electron-lucent cylinders surrounded by an extremely dense calcified matrix. In the third pattern (Fig. 7C), the cal-

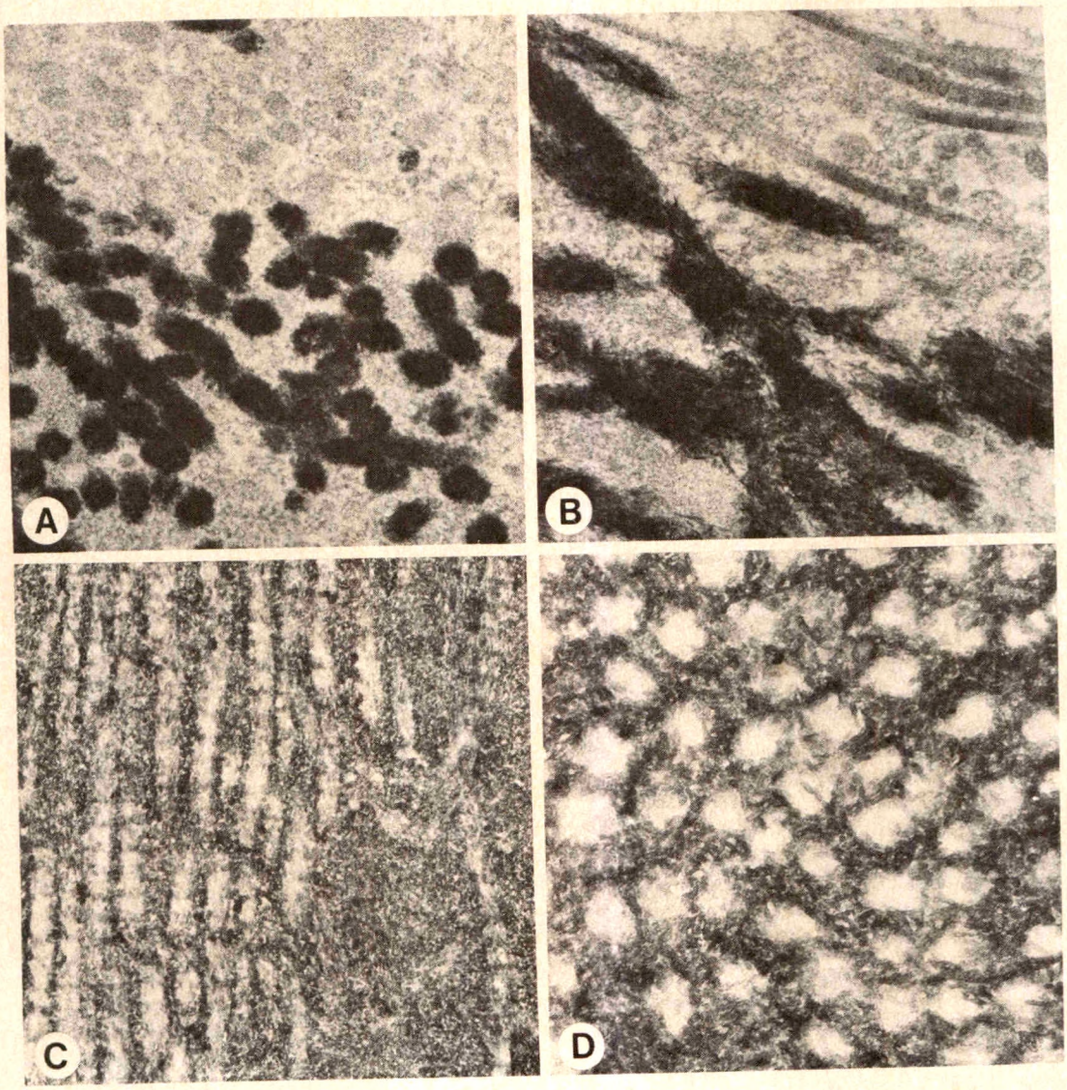


FIGURE 7. High magnification views of calcific deposits associated with collagen fibrils. Case 1, **A** and **C**; Case 3, **B**; Case 6, **D**. **A** and **B**, transverse (**A**) and longitudinal (**B**) views of deposits that involve the entire thickness of the collagen fibrils. In both views the calcified fibrils appear larger than adjacent uninvolved fibrils, suggesting spread of crystal growth into the interfibrillary spaces (×75,000 and ×60,000, respectively, reduced by 20 percent.) **C** and **D**, calcific deposits in both of these areas occupy interfibrillary spaces. In **C** the crystals are also present in the interior of the collagen fibrils, some of which (**upper right**) are barely discernible. In **D**, the crystalline nature of the calcific deposits is evident (×60,000 and ×127,000, respectively, reduced by 20 percent).

cific deposits occupied both the interfibrillary spaces and the interior of the fibrils, thus giving the deposits a relatively homogeneous appearance. This homogeneous pattern was characteristically present throughout the central areas of large calcific deposits. In contrast, the interfibrillary pattern was found either at the periphery of large masses or throughout small masses. Involvement of the collagen fibrils with sparing of the interfibrillary spaces was found only in small scattered groups of collagen fibrils, and not in association with large calcific deposits.

Most of the calcific deposits associated with connective tissue showed a crystalline substructure when examined at high magnifications, regardless of their pattern of organization with respect to the collagen fibrils. The crystals were cylindrical in shape and measured from 280 to 330 Å in length and from 65 to 80 Å in width. These crystals often were mixed with material that appeared amorphous even at very high magnification. Energy dispersive X-ray microanalysis revealed the presence of calcium and phosphorus in these crystals, and X-ray diffraction analysis disclosed patterns similar to that of apatite. Degeneration of the collagen (usually of severe degree) was often associated with the calcific deposits, but the most severely degenerated collagen was not necessarily the most calcified, and extensive calcific deposits sometimes were evident in areas where collagen showed little or no change.

Small calcific deposits were occasionally found to overlie mitochondria (Fig. 8A) and rarely, nuclei (Fig. 8B) of porcine cells in the cusps. They were located i areas in which other structures were severely calcifie and they constituted a small fraction of the total c calcific deposits. No structures resembling the "matri vesicles" of other calcifying tissues[23,24] were found i any bioprosthetic cusp.

Calcific deposits associated with vegetations an thrombi were composed of plate- or needle-shape crystals (Fig. 9), which measured up to 80 Å in maxima thickness and up to 1,000 Å in largest diameter. Th smallest of these deposits were located within remnant or "ghosts" of platelets and leukocytes that appeare to have been trapped within a mesh of fibrin strands These deposits usually were within mitochondria. Th fibrin strands were not sites of deposition of calcifi crystals.

Discussion

Features of Calcific Deposits in Porcine Bioprostheses:

Predisposing factors: This study reveals that cal cification of porcine bioprostheses can occur in adult as well as in children, that the most important sites o formation of calcific deposits in both age groups are th connective tissue in the cusps and thrombi and vege tations on the surfaces, and that calcific deposits are a important cause of prosthetic valve dysfunction. Ou findings are in accord with those of previous clinica studies[4–22] of calcification of porcine bioprostheses

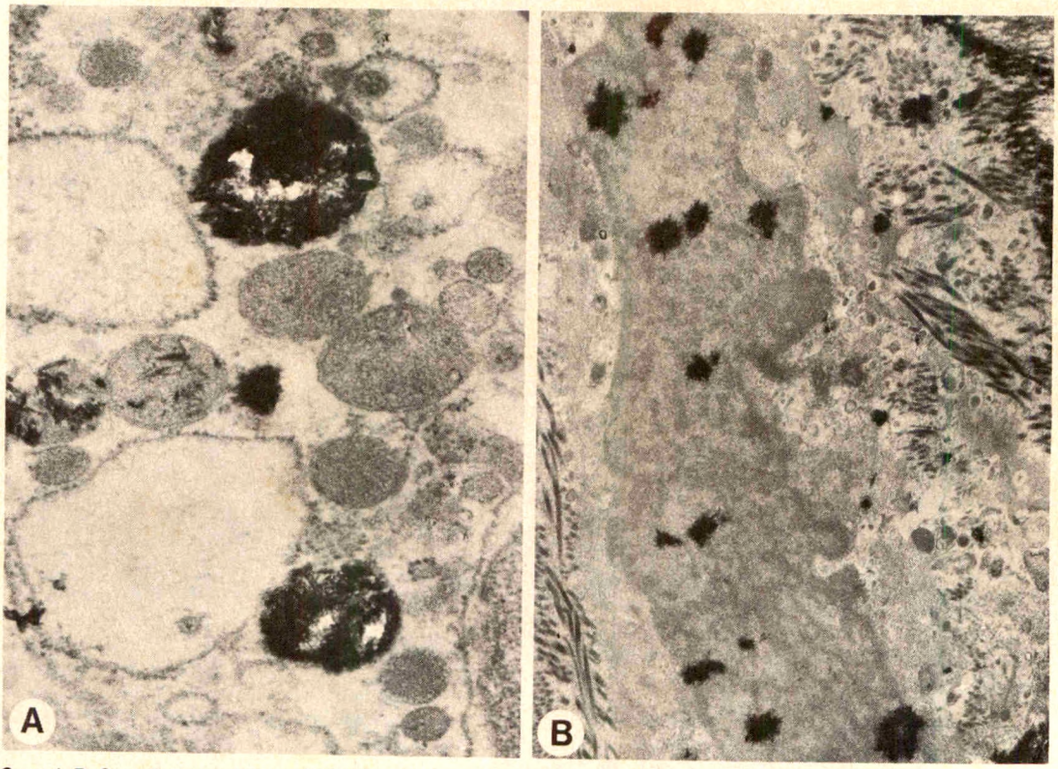


FIGURE 8. A, Case 1; **B,** Case 3. Intracellular calcific deposits in valvular connective tissue cells of porcine origin are few and small, and involved mitochondria (**A**) and nuclei (**B**), (×44,000 [**A**] and ×18,000 [**B**], reduced by 20 percent).

Those studies (Table II) have documented the occurrence of calcification in a total of 37 bioprostheses implanted in 34 patients. The time between implantation and removal of the bioprostheses averaged 28 months, which was less than the mean time of 39 months in our patients. This difference reflects the greater number of children in Table II than in our group of patients. The average age of our patients was 32 years; that of the patients in Table II was 23 years. Although these data indicate that calcification of porcine bioprostheses is more frequent and develops more rapidly in children and young adults than in older patients, our study shows that the gross anatomic, histologic and ultrastructural features of the calcific deposits are the same in both age groups, thus suggesting that the causative processes are similar. Evidence of infection was present in the calcified valves in two of our patients and in seven of the patients previously described (Table II). Metabolic factors that could have contributed to the formation of calcific deposits were identified in only one of our patients and in only three of the patients in Table II; in all four patients, the factor was chronic renal insufficiency.

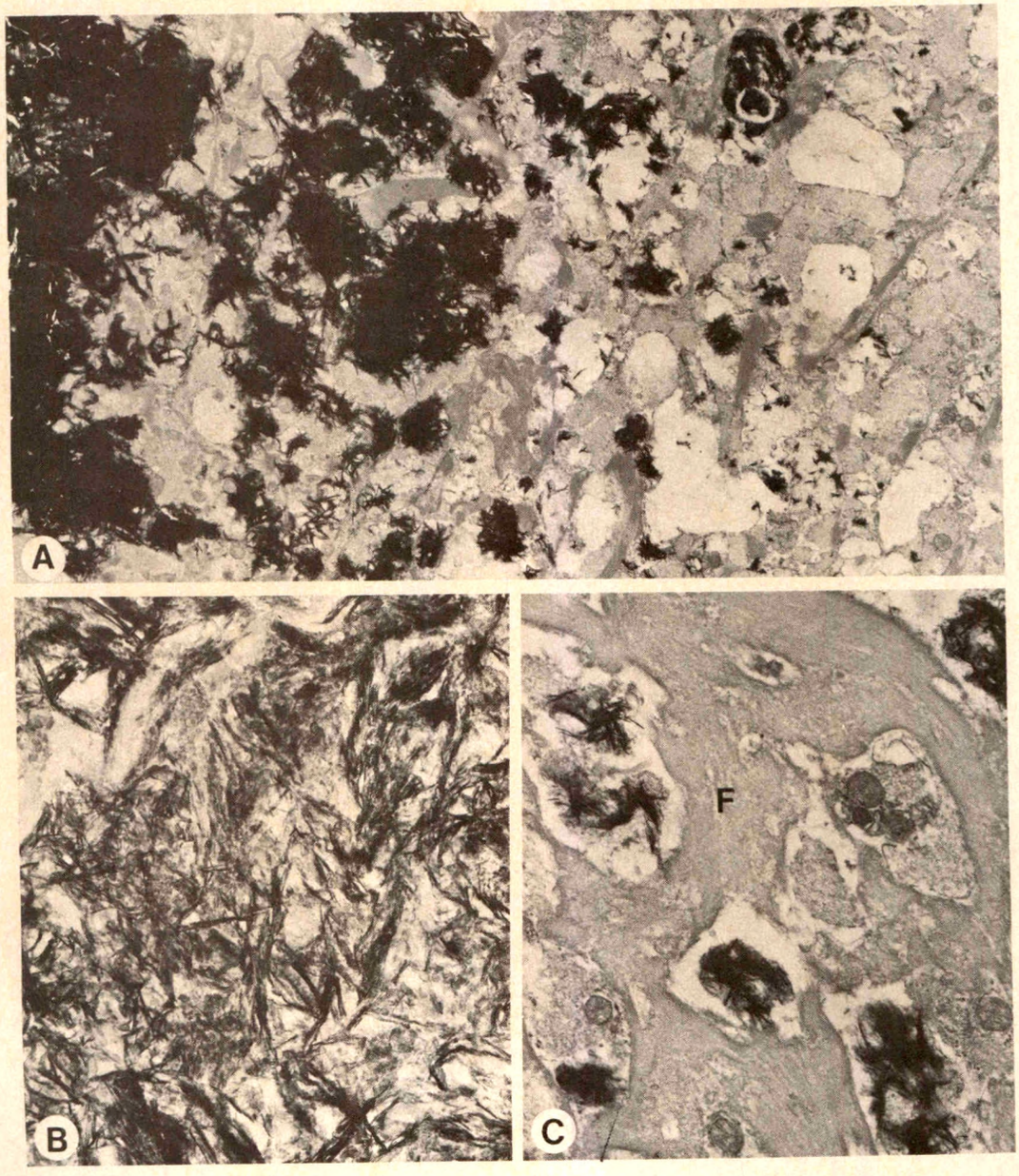


FIGURE 9. Case 8. Calcific deposits associated with thrombotic material on the surface of the bioprosthesis. **A**, low magnification view showin large masses of electron-dense crystals adjacent to thrombus. **B**, high magnification view demonstrating the plate-like structure of the crystal shown in **A**. **C**, remnants of platelets trapped in fibrin mesh (F) contain calcific deposits. (×13,000 [**A**], ×25,700 [**B**], ×37,000 [**C**], reduced b 20 percent.)

Thus, coexisting metabolic disorders are not recognizable in the majority of patients in whom calcific deposits develop in porcine bioprostheses.

Frequency: Such deposits are common. The 14 calcified bioprostheses reported in our study represent nearly 50 percent of all bioprostheses examined with electron microscopy in our laboratory. Because these bioprostheses were submitted for study for a variety of reasons, they do not constitute a representative sample of all implanted porcine bioprostheses. Nevertheless, in the only large institutional experience thus far reported, Billingham et al.[25] observed calcific deposits in 17 (34 percent) of 50 porcine bioprostheses recovered at Stanford University Hospital between 1974 and 1978. Failure to detect calcific deposits may be related to the fact that histologic sections of these bioprostheses usually are taken from the central portions of the cusps. Because the earliest deposits are most frequently located near the commissures, such deposits may be missed. In our experience, the most sensitive technique for detecting calcific deposits in porcine bioprostheses is X-ray examination of the entire explanted bioprosthesis.

Valve dysfunction: Factors such as size and location will determine whether the calcific deposits cause bioprosthetic dysfunction. Recent observations indicate that significant degrees of bioprosthetic stenosis related to calcification of porcine bioprostheses can occur in relatively asymptomatic patients.[26] This clinical situation parallels that which is well known to occur in stenosis affecting natural mitral values. Therefore, the lack of symptoms does not exclude the possibility of significant bioprosthetic stenosis.

Mechanisms of Calcific Deposits

Calcific deposits have been found in porcine bioprostheses implanted in experimental animals[27,28] as well as in other types of bioprostheses implanted in patients, including dura mater valves,[29] fascia lata valves,[28,30–33] porcine valves treated with formalin,[5] periodate[34] or mercuric salts,[5] fresh[28,35] or glutaraldehyde-treated[36] pericardial bioprostheses, and homografts preserved by antibiotics, beta-propriolactone, freeze-drying or irradiation.[37–42] In addition, calcific deposits involving thrombotic material deposited on the sewing ring[43] or on Teflon® cusps[35] also have occurred

TABLE II

Reports of Calcific Deposits in 37 Glutaraldehyde-Treated Porcine Bioprostheses Implanted in 34 Patients

Reference (first author)	PB (n) With Ca^{++}	Age (yr) at PB Implantation	Sex	Type of Heart Disease	Site of PB	PB Removal		Factors Predisposing to Ca^{++}
						Time (mo)	Cause	
Carpentier[4]	4	. . .	. . .	. . .	A	60	Death	. . .
		. . .	. . .	. . .	PC	16	Death	. . .
Zylberberg[5]	1	. . .	. . .	. . .	. . .	18	. . .	. . .
McIntosh[6]	1	. . .	. . .	. . .	m	56	. . .	. . .
Zuhdi[7]	6	. . .	. . .	. . .	. . .	. . .	IE	Infection
Magilligan[8]	2	. . .	. . .	. . .	A, m	36	Death	Infection
Levitsky[9]	1	8	. . .	. . .	. . .	19	Death	
Fishbein[10]; Cohn[17]	2	35	M	. . .	A, m	6	Death	Renal failure
Albert[11]	2	. . .	. . .	. . .	A	61	Stenosis	. . .
		. . .	. . .	. . .	m	12	Stenosis	. . .
Thiene[12]	3	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Forfar[13]	1	26	M	Endocarditis	m	0.5	Stenosis	. . .
Rose[14]	1	13	F	. . .	m	12	Death	. . .
Hetzer[15]	1	64	F	. . .	m	2	Death	Renal failure
Kutsche[16]	3	8	F	MR (cong)	m	58	Stenosis	. . .
		12	M	MR (cong)	m	43	Stenosis	. . .
Platt[18]	1	50	M	. . .	. . .	33	Death	. . .
Geha[19]	5	9.5	F	AR	A	26	Stenosis	. . .
		9	F	AS (cong)	A	45	Stenosis	. . .
		16	M	AS	A	41	Stenosis	. . .
		5	M	MR	m	22	Stenosis	. . .
Lamberti[20]	3	18	F	MR	m	31	Stenosis	. . .
		45	F	MR, TR	m, T	16	Death	Renal failure
Total	37 (34 pts)	23 (average)	M 6; F 7		m 12; A 7; T 1; PC 1	28 (average)	Stenosis 10; IE 6; death 11	Renal failure 3; infection 7

A = aortic valve; AR = aortic regurgitation; AS = aortic stenosis; Ca^{++} = calcium; cong = congenital; IE = infective endocarditis; m = mitral valve; MR = mitral regurgitation; PB = porcine bioprosthesis; PC = pulmonary conduit; pts = patients; T = tricuspid valve; TR = tricuspid regurgitation; . . . = information not available.

in rigid-framed valves. The actual frequency of these changes has not been studied and the histologic features of calcific deposits in prosthetic heart valves have been the subject of few studies. The aortic wall in homografts has been reported to undergo much more severe calcification than the cusps.[40,44,45] The localization of calcific deposits in valve bioprostheses has not been studied in detail, although calcified collagen has been observed in variously prepared porcine bioprostheses.[5] In this study, several sites of calcification were identified in porcine bioprostheses. Among these were collagen, organized thrombi and vegetations, mitochondria and nuclei of cells of porcine origin, and the cytoplasm of adipose tissue cells. Of these sites, collagen and thrombotic material appeared to be the most important; the deposits at these sites represent the results of different mechanisms and therefore will be considered separately.

Calcification of collagen: The process of normal calcification of tissues such as bone, cartilage and teeth basically consists of the deposition of a crystalline inorganic phase, composed of a form of calcium phosphate known as hydroxyapatite, on a preexisting matrix of collagen fibrils that are associated with proteoglycans (complexes of proteins and acid mucopolysaccharides), noncollagen glycoproteins, peptides, lipids and other components of connective tissue ground substance.[46,47] The calcium and phosphate ions are derived from the circulating blood and can come into contact with the calcifying matrix either directly, by simple diffusion or after being absorbed and concentrated within connective tissue cells.[46]

The nature of the initial sites of formation of calcific deposits in the organic matrix of calcifying connective tissues is still the subject of controversy, although there is complete agreement that the end result, calcification of collagen, is similar regardless of the initial events. In early stages of development of bone, cartilage and dentine, the process of calcium deposition is initiated by structures known as matrix vesicles.[23,24] These vesicles are secreted by connective tissue cells, are limited by single trilaminar membranes and contain small needle-shaped crystals of calcium phosphate. These crystals grow in size as the membranes of the matrix vesicles rupture, and extension and coalescence of crystal growth lead to calcification of the collagen. In many instances other than early development, the process of calcification of collagenous structures occurs without participation of matrix vesicles, and in these instances the collagen itself becomes the site of formation and growth of nuclei of crystallization.[46,47] This mechanism appears to be responsible for calcification of connective tissue in porcine bioprostheses, in which we found no matrix vesicles. Porcine valve connective tissue cells cannot participate in a process of secretion of matrix vesicles, because these cells are killed by the commercial processing of glutaraldehyde. Direct involvement of collagen in the formation of calcific deposits also is suggested by our finding of small foci of calcium phosphate crystals overlying collagen fibrils. The morphologic features of calcified collagen in porcine bioprostheses are similar to those of calcific deposits occurring spontaneously and induced experimentally, both in vivo and in vitro, in collagen in tendons of animals[48–53] and in skeletal muscle of human beings with fibrositis (myositis) ossificans.[48]

The initial deposits of calcium in mineralizing connective tissues consist of amorphous calcium phosphate; this amorphous material is gradually transformed into crystalline hydroxyapatite.[52,53] The current concepts of the relation of the collagen to the calcific deposits are that (1) phosphate groups form covalent bonds that connect the organic and inorganic components in calcified tissues; (2) epsilon-amino groups present in lysine and hydroxylysine are of importance in forming the bonds between native collagen and phosphate groups; (3) many of the hydroxylysine residues normally are either linked (glycosylated) to noncollagen carbohydrate material or modified to form covalent cross-links; and (4) the three dimensional structure of the collagen fibril is also of importance in determining the availability of these groups for reacting with phosphate and serving as centers of nucleation.[46,53] Thus, all collagen appears to be theoretically capable of calcifying. The reason that many areas of collagen do not calcify in vivo has been attributed to the presence in the ground substance in such areas of proteoglycans and glycoproteins, which are associated with collagen[53,54] and which mask or block the sites that would react with phosphate and calcium to become nucleation centers.[53] This concept appears to be applicable to the calcification of collagen in porcine valve bioprostheses. This calcification is most marked in the spongiosa, the layer that in the native porcine valve is most abundant in proteoglycan material. We[2] have previously shown that this material is lost after commercial processing and implantation, and we believe that this loss of proteoglycan may predispose to calcification for two reasons. The first reason is the uncovering of phosphate-binding sites in the collagen, as previously mentioned. The second reason is the loss of proteoglycan, leaving empty spaces in the spongiosa; these spaces may become filled with deposits of plasma proteins and other blood constituents, which in turn may provide additional sites of calcification.

The possible participation of other proteins in calcification of collagen is suggested by the recent identification of several different classes of proteins that have a high binding affinity for calcium.[55–59] This binding affinity is related to their content of gamma-carboxyglutamic acid, an unusual amino acid that is formed by a reaction that requires vitamin K and bicarbonate. Some of these proteins (the vitamin K-dependent blood clotting proteins) are present in normal blood; others have been found in tissues undergoing normal (bone) or abnormal (renal calculi, atherosclerotic plaques, skin in scleroderma and dermatomyositis) calcification.[55–57] Levy et al.[58,59] found gamma-carboxyglutamic acid in hydrolysates of protein material extracted from porcine bioprostheses that had manifested calcific deposits after being implanted in patients and from calcified native aortic valves, but not from noncalcified bioprostheses. The origin (from circulating blood or from in situ synthesis), the localization in the

bioprosthetic tissue and the significance of this protein material in porcine valves have not yet been established. Nevertheless, these findings are important because they represent a new, incompletely understood aspect of biologic calcification.

The role of pretreatment with glutaraldehyde in modifying the tendency of porcine bioprostheses to undergo calcification is unclear. Such pretreatment introduces several additional cross-links in collagen, thus stabilizing the structure of the fibrils. This finding suggests that the inability of calcium and phosphate to penetrate into the highly cross-linked interior of the collagen fibrils may explain why calcific deposits often (Fig. 7, C and D) do not extend into the cores of collagen fibrils in porcine bioprostheses. Such penetration would result in complete calcification of the collagen fibrils (Fig. 7, A and B), which was a less frequent microscopic finding in our study. Glutaraldehyde reacts in a complex manner with free amino groups in lysine and hydroxylysine,[60] thus possibly preventing them from reacting with phosphate to initiate the formation of calcific deposits. However, it is probable that new lysine and hydroxylysine residues (or other reactive residues) are brought into the tissue after implantation through plasma proteins that penetrate between collagen fibers and permeate the connective tissue framework. A large incidence of calcification developed in porcine bioprostheses that had been prepared for clinical use by treatment first with sodium metaperiodate, a mild oxidizing agent,[61] and ethylene glycol and then with glutaraldehyde.[34] The exact relation between this oxidative process and the subsequent development of calcification has not been clarified. It is known from other observations[46,62] that the process of calcification of biologic materials is subject to considerable modifications by a wide variety of agents, including hormones (parathormone and calcitonin), vitamin D and alkaline phosphatase (an enzyme that hydrolyzes various phosphate esters and thus generates inorganic phosphate, which contributes to calcification). Thus, calcification of collagen in porcine bioprostheses tends to be most marked in children, in whom the balance of hormonal and metabolic factors clearly favors the deposition of calcium phosphate in collagen in other tissues such as bone. A predisposition to calcification of soft tissues is well known to occur in patients with chronic renal disease and secondary hyperparathyroidism.[63]

Calcification of thrombotic material: Thrombi in various sites are known to calcify, most notably in the left atrium of adults with mitral stenosis. The mechanisms of formation of calcific deposits in thrombi have not been studied ultrastructurally. Our observations show that the sites of initial calcification in thrombi and vegetations are platelets and leukocytes that become trapped in the fibrin mesh. The intracellular components that undergo calcification are the mitochondria, and crystal growth from these sites leads to the formation of large confluent and calcific masses. These masses in turn probably induce the formation of additional thrombi, and repeated episodes of thrombosis and calcification probably account for the layered or laminated appearance of calcific deposits of this type. As in the case of calcification of collagen, calcification of mitochondria represents a commonly occurring biologic phenomenon. Mitochondria are the sites of calcification in ischemic heart muscle cells[64,65] and in other cell types in many other conditions.[66] Thus, mitochondrial calcification constitutes a basic mechanism for the initiation of intracellular calcification, and from mitochondria the deposits can spread and fill the entire cell. This mechanism is important with respect to host cells in surface thrombi, but seems to be operational only to an extremely limited extent in the porcine cells in bioprostheses. Perhaps this is so because the accumulation of calcium in mitochondria, at least in its initial stages, is an active process that occurs in cells that may be injured but are still alive.[66] This process excludes porcine cells, which are killed by the glutaraldehyde processing.

Implications: Calcific deposits are commonly found in implanted porcine bioprostheses. In some of these prostheses, particularly in those implanted in children and young adults, they are the cause of important degrees of bioprosthetic dysfunction. They can be caused by calcification of cuspal collagen or of thrombotic material on the cuspal surfaces. An understanding of the mechanisms of formation of these two types of deposits is essential for the formulation of measures designed to prevent calcification of tissue valves.

Addendum

Four very recent reports[67–70] have provided additional documentation of the occurrence of early, severe calcification of porcine valve bioprostheses implanted in children and young adults without metabolic diseases or infective endocarditis. In some patients[68,69] the calcification was associated with degeneration of collagen. It was suggested[69] that this calcification may be promoted by host factors related to calcium homeostasis.

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Chronic Intravascular Hemolysis After Aortic Valve Replacement With Ionescu-Shiley Xenograft: Comparative Study With Bjork-Shiley Prosthesis

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Twenty patients with a prosthetic valve (Ionescu-Shiley or Bjork-Shiley) in the aortic position were studied for evidence of intravascular hemolysis. Serum lactic dehydrogenase and serum haptoglobin levels were used as the most sensitive indicators of hemolysis. Elevated concentrations of lactic dehydrogenase were found in all 10 patients with an Ionescu-Shiley prosthesis (mean 402 IU/liter) and in 7 of 10 patients with a Bjork-Shiley prosthesis (mean 234 IU/liter). The mean serum haptoglobin was 15 mg/dl (range 10 to 28) in patients with the Ionescu-Shiley valve and 96 mg/dl (15 to 284) for those with the Bjork-Shiley valve. This study indicates the presence of chronic intravascular hemolysis in patients with the Ionescu-Shiley aortic valve. The increase in lactic dehydrogenase was significantly greater in patients with the Ionescu-Shiley prosthesis than in those with the Bjork-Shiley prosthesis, indicating a slightly shorter red cell life span in the former group.

Intravascular hemolysis in patients with prosthetic heart valves has been recorded for ball valve and disc prostheses.[1–4] The newer tissue valves have been the subject of fewer studies.[5–7] Recent reports[8–10] have stated that the Ionescu-Shiley pericardial xenograft does not cause detectable hemolysis. In contrast, we[11] have found evidence of hemolysis associated with this prosthesis in the mitral position. In this study we attempted to assess the incidence and severity of hemolysis in 10 patients with the Ionescu-Shiley xenograft in the aortic position. The results were compared with those found in 10 patients with a Bjork-Shiley aortic valve disc prosthesis.

Methods

Patients: Twenty patients (14 men and 6 women) who had undergone aortic valve replacement were studied; of these, 10 patients had valve replacement with the Ionescu-Shiley xenograft and 10 with the Bjork-Shiley prosthetic valve. In the group with the Ionescu-Shiley valve, the hematologic studies were performed at a mean interval of 10.6 months (range 3 to 16) after aortic valve replacement; five valve sizes (anulus diameter 19, 21, 23, 25 and 27 mm) were used. The mean age of the patients in this group was 53.8 years (range 20 to 72). The group with the Bjork-Shiley valve was studied at a mean interval of 31 months (range 3 to 48) after operation; three valve sizes (anulus diameter 21, 23 and 25 mm) were studied. The mean age of the patients in this group was 58.5 years (range 47 to 65).

Of the 10 patients with an Ionescu-Shiley valve, 9 underwent postoperative hemodynamic and angiographic investigations; 8 of the 9 had a competent valve, and all had a small transvalve gradient. One patient had a grade I/IV paravalve leak.

Laboratory studies: To assess hemolysis, the following laboratory tests were performed: a complete blood count with reticulocyte count, platelet count, red cell indexes and examination of the blood smear. Other studies included determination, by standard methods, of serum haptoglobin, serum lactate dehydro-

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TABLE I

Comparison of Hematologic Variables in 10 Patients With the Ionescu-Shiley and 10 With the Bjork-Shiley Aortic Prosthesis

	Serum LDH (IU/liter)	SGOT (IU/liter)	Serum Haptoglobin (mg/dl)	Hemoglobin (g/100 ml)	Hematocrit (%)	Reticulocyte Count (%)
Normal range	90–215	10–50	170–300	12.5–18	38 to 52	<2
Ionescu-Shiley						
Mean	402	37	15	13.8	40	2.3
Range	294–580	28–48	10–28	12.5–16	8–46	0.5–5.6
Bjork-Shiley						
Mean	234	31	96	14.5	42	0.8
Range	178–287	24–37	15–284	13.1–16	38–47	0.5–1.0
p value	<0.05	NS	<0.05	NS	NS	<0.05

LDH = lactic dehydrogenase; n = number; NS = not significant; p = probability (p <0.05 = significant); SGOT = serum glutamic oxaloacetic transaminase.

genase with isoenzymes, serum glutamic oxaloacetic transaminase (SGOT) and total bilirubin concentration. Serum iron, total iron-binding capacity, iron saturation, urine hemosiderin were also measured and Coombs' test was performed.

Clinical features: Clinical assessment of all patients, together with hemodynamic and angiographic evaluation (9 of the 10 patients with an Ionescu-Shiley valve), revealed no apparent contributory cause of the hemolysis, with the exception of a mild grade (I/IV) paravalve leak in one patient with the Ionescu-Shiley valve; in addition, one patient with the latter valve had a sinus of Valsalva aneurysm repaired with a Dacron® patch. There were no recent episodes of myocardial infarction by clinical or electrocardiographic evidence. The patients showed no evidence of autoimmune disease (negative Coombs' test). Hence, any intravascular hemolysis was wholly attributable to the prosthesis in most patients.

Student's t *test was used for statistical evaluation of the results.* Probability (p) values greater than 0.05 were considered not statistically significant.

Results

Serum lactic dehydrogenase: Laboratory data obtained from patients with the two types of aortic valve prosthesis are summarized in Table I and Figure 1. The mean value for serum lactic dehydrogenase in patients with an Ionescu-Shiley valve (402 IU/liter) was significantly ($p < 0.05$) greater than the mean value for patients with a Bjork-Shiley valve (234 IU/liter). In the latter group, lactic dehydrogenase values were only slightly higher than the normal range. The highest value (580 IU/liter) was obtained in a patient with an Ionescu-Shiley valve who had the mild paravalve leak.

Serum haptoglobin: Reduced serum haptoglobin was found in 100 percent of patients with an Ionescu-Shiley prosthesis (less than 50 mg/dl in all cases), but in only 80 percent of patients with a Bjork-Shiley valve (two patients had normal values). Mean values for haptoglobin were lower than normal in both patient

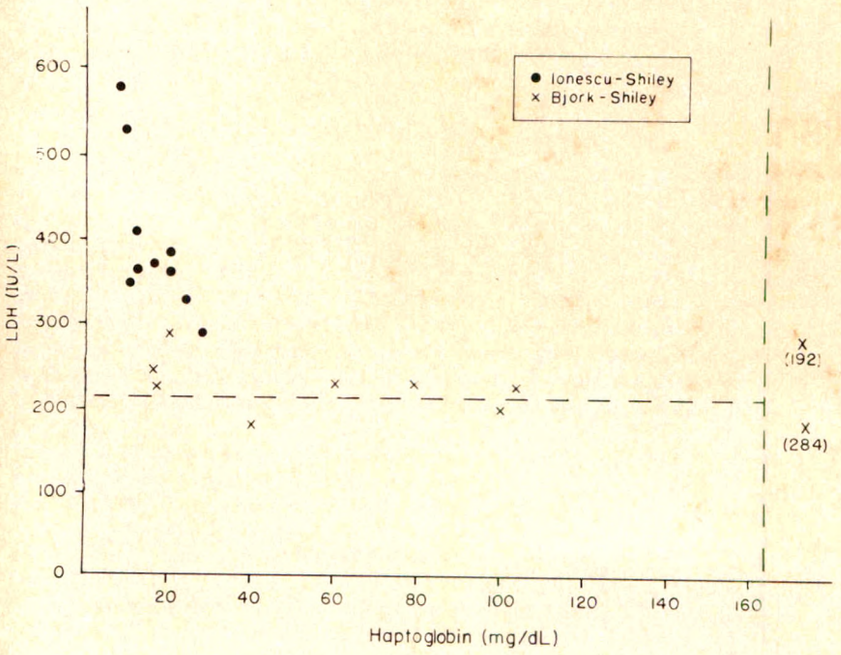


FIGURE 1. Plot diagram showing the relation between serum lactic dehydrogenase (LDH) and haptoglobin values in patients with the Ionescu-Shiley or Bjork-Shiley prosthesis. The **horizontal interrupted line** marks the upper normal range for lactic dehydrogenase, and the **vertical interrupted line** marks the lower normal range for haptoglobin.

groups (Table I). In patients with the Ionescu-Shiley valve, elevated lactic dehydrogenase values were always associated with reduced haptoglobin. In the group with the Bjork-Shiley valve haptoglobin was reduced in some patients in spite of normal lactic dehydrogenase values (Fig. 1).

Relation to valve size: The relation between valve size and values for lactic dehydrogenase and serum haptoglobin is shown in Figures 2 and 3, respectively. The degree of hemolysis as measured by either value apparently had no direct relation to valve size in any of the two prostheses evaluated.

Other signs of hemolysis: Hemoglobin concentrations (Table I) were definitely but not significantly lower in patients with an Ionescu-Shiley prosthesis. Reticulocyte counts were raised in four patients with an Ionescu-Shiley prosthesis (2.1, 2.8, 3.0, and 5.6, respectively). In the group with the Bjork-Shiley prosthesis hemolysis was so slight that reticulocyte counts were normal in all. One patient with an Ionescu-Shiley valve and a mild paravalve leak had hemosiderinuria. This patient also had the highest lactic dehydrogenase value (580 IU/liter). Bilirubin values were normal in all patients except one with an Ionescu-Shiley valve who had a marginally raised level.

Other laboratory values: The Coombs' test was negative in all patients in both groups. This finding suggests that no immune mechanism was involved in the hemolytic process. Serum glutamic oxaloacetic transaminase, serum iron, total iron binding capacity, peripheral blood smear and platelets were normal in patients in both groups.

Discussion

Hemolysis as a complication of valve replacement: Chronic intravascular hemolysis is a well-known complication of valve replacement and is probably related to the mechanical design of the prosthesis itself.[12] Measurement of serum lactic dehydrogenase (LDH, red cell isoenzyme) is a sensitive method of estimating intravascular hemolysis, and the level correlates well with the shortening of erythrocyte survival time.[13] It was elevated in all patients with an Ionescu-Shiley prosthesis, but in only two thirds of those with a Bjork-Shiley valve. In patients with the former valve, most lactic dehydrogenase values were in the range of 300 to 500 IU/liter, indicating a slightly or only moderately reduced life span of erythrocytes.[13]

Serum haptoglobin levels have been used in previous reports[7] as another index of hemolysis. In our series the haptoglobin levels were greatly decreased in all patients with the Ionescu-Shiley valve and less markedly decreased in those with the Bjork-Shiley valve.

A positive direct Coombs' test has been reported in patients after heart valve replacement. It has been suggested that an immune mechanism may be involved in some cases of hemolysis after valve replacement.[14] In our study the direct Coombs' test was negative in all cases. Therefore, it is unlikely that an immune mechanism played a role in the hemolysis detected in our series.

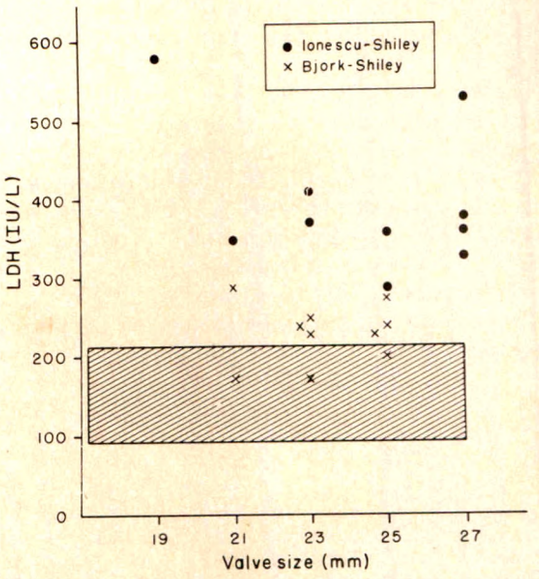


FIGURE 2. Serum lactic dehydrogenase (LDH) values related to valve size and type. The **shaded area** shows the normal range. Valve size is indicated by the valve number given by the manufacturer.

Role of size and type of valve prosthesis: There has been controversy about whether prostheses of the same type cause different degrees of hemolysis in the aortic and mitral position.[12,15] We[11] previously found that the Ionescu-Shiley prosthesis in the aortic position caused slightly greater hemolysis than the same valve in the mitral positon. Similar findings have been reported with the Starr-Edwards prosthesis.[2,15]

Hemolysis has been reported to be dependent on the size of the prosthesis.[4,16] Other investigators[1] have reported no correlation between the degree of hemolysis

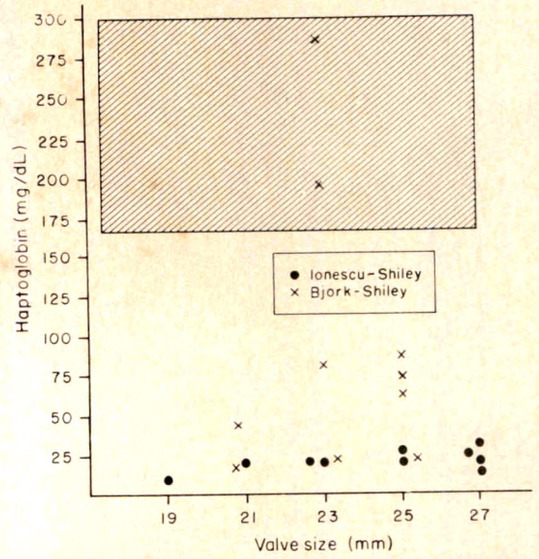


FIGURE 3. Serum haptoglobin values related to valve size and type Conventions as in Figure 2.

and the valve size. We found no direct relation between lactic dehydrogenase, haptoglobin and valve size (Fig. 2 and 3).

There is conflicting evidence concerning the value of increased serum lactic dehydrogenase as an indicator of a paravalve leak.[1,7] In our series, the highest value for lactic dehydrogenase was found in a patient with the only Ionescu-Shiley valve with a mild paravalve leak. Nevertheless, our data are inconclusive in this respect.

Implications: This hematologic study was carried out at a relatively short postoperative time interval in the group with the Ionescu-Shiley valve (mean 10.6 months). Investigators with a longer observation period of patients with other types of prostheses have reported a regression of hemolysis due to endothelialization of the valve structures.[7] If this interpretation is correct, with time one would observe a lesser degree of erythrocyte destruction with the Ionescu-Shiley xenograft than that indicated by our data.

In conclusion, this study has indicated the presence of chronic, mild intravascular hemolysis in patients with the Ionescu-Shiley prosthesis. The findings are suggestive of a significantly greater incidence and degree of hemolysis in patients with this prosthesis than in those with the Bjork-Shiley prosthesis.

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Two Dimensional Echocardiographic Recognition of the Descending Thoracic Aorta: Value in Differentiating Pericardial From Pleural Effusions

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The course of the descending thoracic aorta has recently been visualized with two dimensional echocardiography and its presence confirmed with contrast studies. In the parasternal short axis view, we used the location of the descending thoracic aorta to differentiate pericardial from pleural effusions in 40 patients. Sixteen patients, each with an isolated pericardial effusion, had an echo-free space between the descending thoracic aorta and left ventricular posterior wall. Nine patients, each with an isolated pleural effusion, had an echo-free space posterior to the descending aorta. Fifteen patients, each with both a pericardial and a pleural effusion, had echo-free spaces both between the descending thoracic aorta and left ventricular posterior wall and also posterior to the descending thoracic aorta. With one exception, all patients had anatomic confirmation of these findings. Forty-one patients undergoing cardiac surgery served as controls and none had a posterior echo-free space in relation to the descending thoracic aorta. At operation, no pericardial or pleural effusion was evident. The location of the descending thoracic aorta on two dimensional echocardiography serves as a valuable landmark in localizing the pericardial-pleural interface, thereby differentiating pericardial from pleural effusions.

There may be difficulty in differentiating pericardial from pleural effusions with M mode echocardiography, especially when a large posterior effusion is visualized without a concomitant anterior effusion.[1–3] M mode echocardiography may also be unreliable in differentiating a pericardial from a pleural effusion when the echo-free space extends behind the left atrium. In addition, the presence of a large left atrium may be mistaken for an effusion.[1,2,4–7]

Recently, Mintz et al.[8] visualized the position and course of the descending thoracic aorta with two dimensional echocardiography. Its presence was confirmed by means of an intravascular catheter and injection of indocyanine green or saline. Anatomically, the descending thoracic aorta lies between the pericardium and pleura (Fig. 1, left). Because the descending thoracic aorta is interposed between the pericardium anteriorly and the pleura posteriorly, it may be a useful landmark in the differentiation of posterior effusions.

The purpose of this study is therefore twofold: (1) to observe the spatial relation between the descending thoracic aorta and pericardial and pleural interfaces; and (2) to determine the value of two dimensional echocardiography in differentiating pericardial from pleural effusions by localization of the descending thoracic aorta.

Methods

Study patients: The clinical, chest roentgenographic, electrocardiographic, echocardiographic and pathologic findings in 40 patients with either pericardial, pleural or combined effusions and in 41 control patients were analyzed retrospectively. Sixteen men and 24 women had effusions. They ranged in age from

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12 to 77 years (median age 56.5). Twenty-three men and 18 women constituted the control group. They ranged in age from 19 to 73 years (median age 56).

The patients were separated into four groups: Group I comprised 41 control patients who underwent various cardiac surgical procedures. These patients had no effusions on two dimensional echocardiography and had confirmation of the negative findings at cardiac operation.

Group II comprised 16 patients with an isolated pericardial effusion that was proved at operation in 9 patients and by pericardiocentesis in 6. One patient with congestive heart failure had echocardiographic evidence of an effusion that subsequently disappeared with diuresis. Chest roentgenography showed no pleural effusion in any of these patients.

Group III comprised nine patients with an isolated pleural effusion. The effusion was confirmed by thoracentesis in two patients, at postmortem examination in two and by chest roentgenogram in seven.

Group IV comprised 15 patients with combined pericardial and pleural effusions. Pericardial effusion was confirmed at operation in seven patients, by pericardiocentesis in seven, and by postmorten examination in one patient. Pleural effusion was confirmed by chest roentgenogram in these patients.

Echocardiography: M mode echocardiographic studies were performed in the supine or left lateral decubitus position using either a Smith-Kline Ekoline 20A ultrasonoscope interfaced with an Irex 101 Continutrace recorder or an Irex System II ultrasonoscope. Two dimensional echocardiographic studies were performed in the supine or left lateral decubitus position using a Varian V3000 or a Grumman RT-400 phased-array sector scanner. The M mode echocardiographic study consisted of a standard longitudinal sweep from the aorta to below the level of the mitral valve leaflets. The two dimensional echocardiographic study consisted of a parasternal long axis view and a series of continuous parasternal short axis views from the level of the aortic leaflets to the left ventricular apex. In the parasternal long axis view, the descending thoracic aorta appeared as a pulsatile echo-free space in the posterior atrioventricular groove.[8] In the parasternal short axis view, the descending thoracic aorta appeared as a circular or oval echo-free space at the level of the mitral leaflets and papillary muscles. At this level, the descending thoracic aorta was located directly behind the left ventricle.[8] At the level of the left atrium, the descending thoracic aorta was located directly behind the left ventricle.[8] At the level of the left atrium, the descending thoracic aorta was visualized lateral to and behind the left atrium.

During both M mode and two dimensional echocardiographic studies, gain and reject settings were adjusted for maximal far field resolution and definition. Images were recorded on videotape for later playback and analysis. This analysis was performed at real time speed, slow motion speed and stop action. The images presented on the screen were reproduced with Polaroid® photographs.

Results

Group I: The 41 control patients underwent open heart surgical procedures. These included, alone or in combination, saphenous vein-coronary bypass, ventricular aneurysmectomy, mitral or aortic valve replacement, mitral valve commissurotomy, tricuspid valve replacement and closure of atrial septal defect. Each patient was found to have physiologic amounts of fluid (less than 16 ml) or no pericardial fluid at the time of operation.

M mode studies were performed in 28 patients. Twenty-six studies showed no echo-free spaces. Two studies demonstrated the presence of a small posterior echo-free space. None of the 41 control patients had a pericardial or pleural effusion on the two dimensional study. Figure 1, right, shows the two dimensional echocardiogram of a control patient. The descending thoracic aorta was visualized directly behind the left

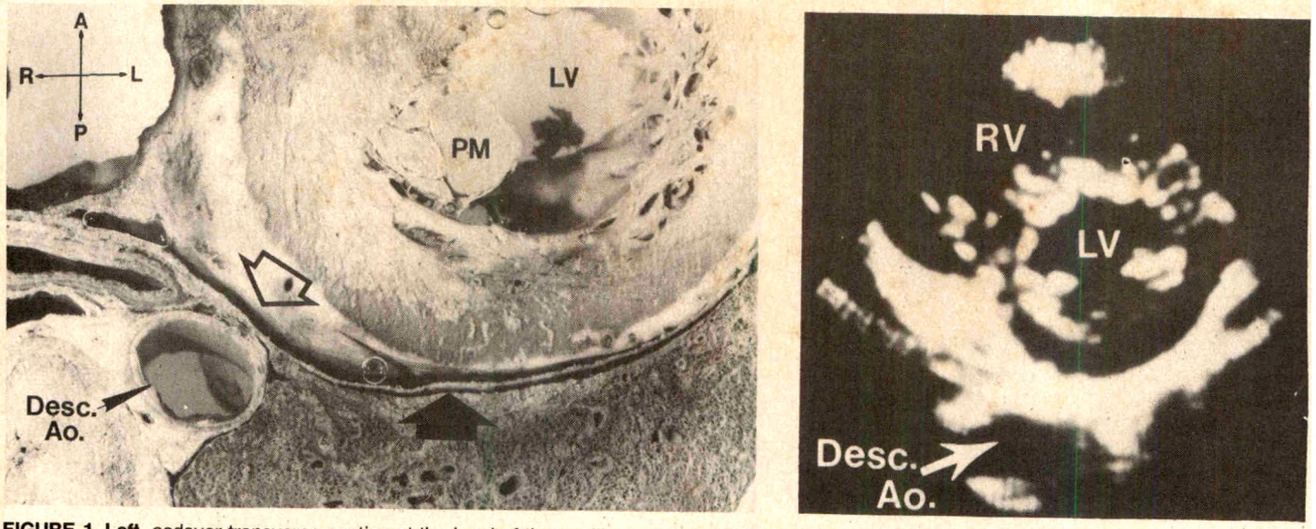


FIGURE 1. Left, cadaver transverse section at the level of the papillary muscles (PM) demonstrating the relation of the posterior pericardium (**open arrow**), left pleural space (**dark arrow**), and lung to the descending thoracic aorta (Desc. Ao.). **Right,** two dimensional echocardiographic parasternal short axis view in a normal subject. Orientation is similar to that in the panel at left. No pericardial or pleural effusion is present, and there is no separation of the descending thoracic aorta from the left ventricular (LV) posterior wall. A = anterior; L = left; P = posterior; R = right; RV = right ventricle.

ventricle in the parasternal short axis view. No echo-free space was visualized either anterior to or posterior to the descending thoracic aorta.

Group II: These 16 patients had isolated pericardial effusion due to malignancy (4 patients), congestive heart failure (3), postoperative hemopericardium (3), idiopathic causes (2), uremia (1), Dressler's syndrome (1), myxedema (1) and infection (1). Cardiomegaly was present on chest roentgenography in 14 patients. The surface electrocardiogram demonstrated low voltage (less than 0.5 mV) in the limb in only four (25 percent) of these patients.

M mode echocardiograms, performed in 15 of the 16 patients, revealed anterior and posterior echo-free spaces compatible with a pericardial effusion in 13. One patient had a large posterior echo-free space without an anterior effusion; the echo-free space extended behind the left atrium and left ventricle. One other patient had no echo-free space visualized.

All 16 patients demonstrated a pericardial effusion on the two dimensional echocardiographic study. In all, the echocardiographic pattern demonstrated in the parasternal short axis view was similar: An echo-free space was visualized anterior to the descending thoracic aorta (Fig. 2), interposed between the aorta and the left ventricular posterior wall. The normal spatial relation between the left ventricular posterior wall and descending thoracic aorta was altered. A distinct separation of these structures was present as the pericardial fluid appeared to push the heart anteriorly in the mediastinum or to push the aorta posteriorly away from the heart. No echo-free space was present behind the descending thoracic aorta.

Group III: These nine patients had isolated pleural effusion due to post-thoracotomy status (four patients), congestive heart failure (three), malignancy (one) and radiation therapy (one). Five patients demonstrated cardiomegaly, and seven patients demonstrated pleural effusion on chest roentgenography. The surface electrocardiogram showed low voltage in two patients.

M mode echocardiograms, performed in eight of the nine patients, revealed a posterior echo-free space without an anterior echo-free space in five; three patients had no posterior echo-free space.

The two dimensional echocardiographic study demonstrated a posterior pleural effusion in all nine patients. In the parasternal short axis view, all patients had an echo-free space visualized posterior and lateral to the descending thoracic aorta (Fig. 3). The fluid was therefore localized behind the descending aorta and left ventricular posterior wall. The normal spatial relation between the descending thoracic aorta and left ventricular wall was preserved. No echo-free space was visualized anterior to the descending thoracic aorta.

Group IV: These 15 patients had combined pericardial and pleural effusions due to postoperative status (3 patients), congestive heart failure (3), uremia (3), radiation therapy (2), malignancy (2), drug therapy (1) and benign tumor (1). On chest roentgenography 8 patients demonstrated cardiomegaly, and all 15 patients

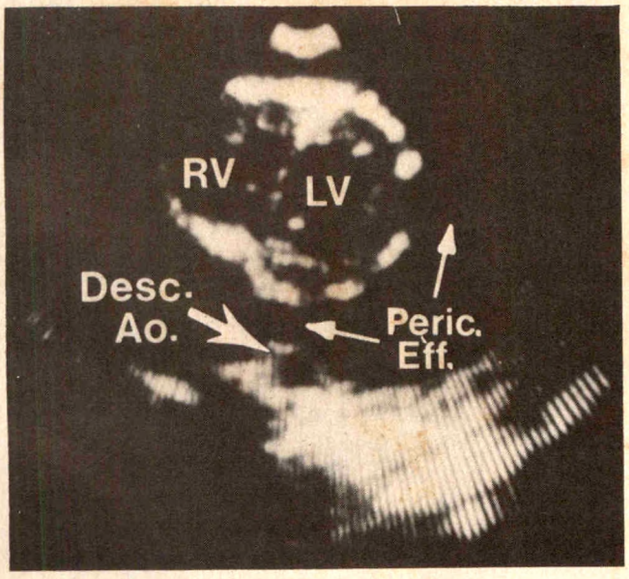


FIGURE 2. Two dimensional echocardiographic parasternal short axis view in a patient with a posterior pericardial effusion (Peric. Eff.). The pericardial effusion appears as an echo-free space anterior to the descending thoracic aorta (Desc. Ao.). A distinct separation of the descending aorta and left ventricular (LV) posterior wall is present. RV = right ventricle.

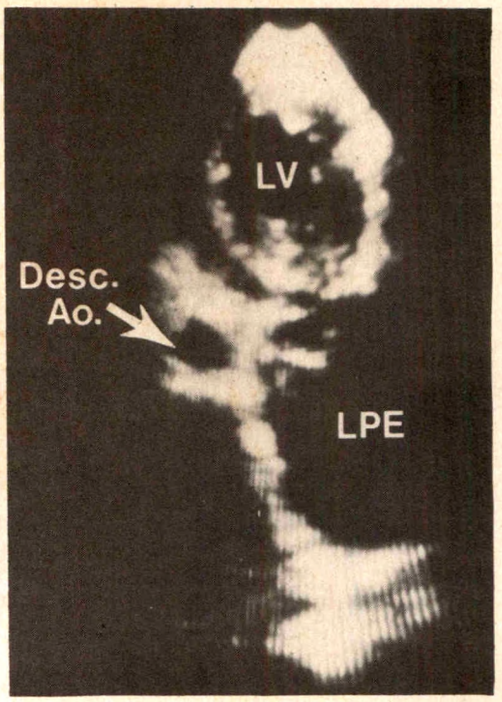


FIGURE 3. Parasternal short axis view in a patient with an isolated left pleural effusion (LPE). The effusion appears as an echo-free space posterior and lateral to the descending thoracic aorta (Desc. Ao.). Anterior to the aorta the left ventricular (LV) posterior wall is seen. It consists of a dense pericardium separated from the endocardium by a relatively echo-free zone of myocardium. This should not be misinterpreted as a pericardial effusion.

had a pleural effusion. The surface electrocardiogram demonstrated low voltage on the limb leads of four patients.

M mode echocardiograms, performed in all 15 patients, revealed definite pericardial effusion in 12 (80 percent; however, 3 patients (20 percent) demonstrated a posterior echo-free space that could not be differentiated from a pleural effusion.

The two dimensional echocardiographic study demonstrated both pericardial and pleural effusions in all 15 patients. The echocardiographic pattern in all patients was similar: In the parasternal short axis view, an echo-free space was visualized both anterior to and posterior and lateral to the descending thoracic aorta (Fig. 4). Therefore, features of both pericardial and pleural effusions were present. The spatial relation between the aorta and left ventricular posterior wall was altered as in patients in Group II. The heart appeared to be pushed anteriorly or the descending thoracic aorta to be pushed posteriorly by the echo-free space. As in patients in Group III there was also an echo-free space seen posterior and lateral to the descending thoracic aorta.

Discussion

The clinical utility of M mode echocardiography in detecting pericardial effusion was recognized in the 1960s by Feigenbaum et al.[9–12] More recent data by Horowitz et al.[13] showed that M mode echocardiography is extremely sensitive and can detect as little as 20 ml of pericardial fluid.

Limitations of M mode echocardiography in diagnosis of pericardial effusion: Certain pitfalls have been recognized in the diagnosis of a pericardial effusion by M mode echocardiography.[2,8] Large pleural effusions, pulmonary infiltrates, a large left atrium, and tumors have all been reported to simulate a pericardial effusion in the M mode echocardiogram.[1,2,7,14–17] Although fluid visualized posterior to the left atrium is generally diagnostic of a pleural effusion, the left oblique sinus (pericardial reflection over the great vessels) is a potential space for an accumulation of pericardial fluid. Several investigators[1,2,5,6] have demonstrated the presence of a pericardial effusion behind the left atrium with M mode echocardiography. The descending thoracic aorta itself has been visualized behind the left ventricular posterior wall as an echo-free space, thus simulating a pericardial effusion.[8] Conversely, pericardial fluid may be present and yet be undetected in the M mode echocardiogram because of a loculated pericardial effusion or too medial a transducer angulation.[2,3,5,6,18,19]

In our study, 83 percent of the M mode studies were diagnostic in patients with a pericardial effusion. In 17 percent there was some difficulty in differentiating between a pericardial and pleural effusion.

Advantages of two dimensional echocardiography: The presence of a pericardial effusion, superior to the atrioventricular groove and visualized behind the left atrium, has been demonstrated with two-dimensional echocardiography by Martin et al.[4] All of their patients with a quantitatively large effusion had a posterior echo-free space behind the left atrium. Two dimensional echocardiography has also been reported to be of clinical value in detecting an isolated pericardial effusion when the M mode study was equivocal.[18] Two dimensional echocardiography, as compared with M mode echocardiography, facilitates study of posterior structures because of improved spatial orientation.[4,8] Only recently has it been appreciated that the descending thoracic aorta could be consistently visualized in a posterior location with two dimensional echocardiography.[8,19–21]

In this study, the descending thoracic aorta was a valuable landmark in differentiating pericardial from pleural effusions. The left parasternal short axis ap-

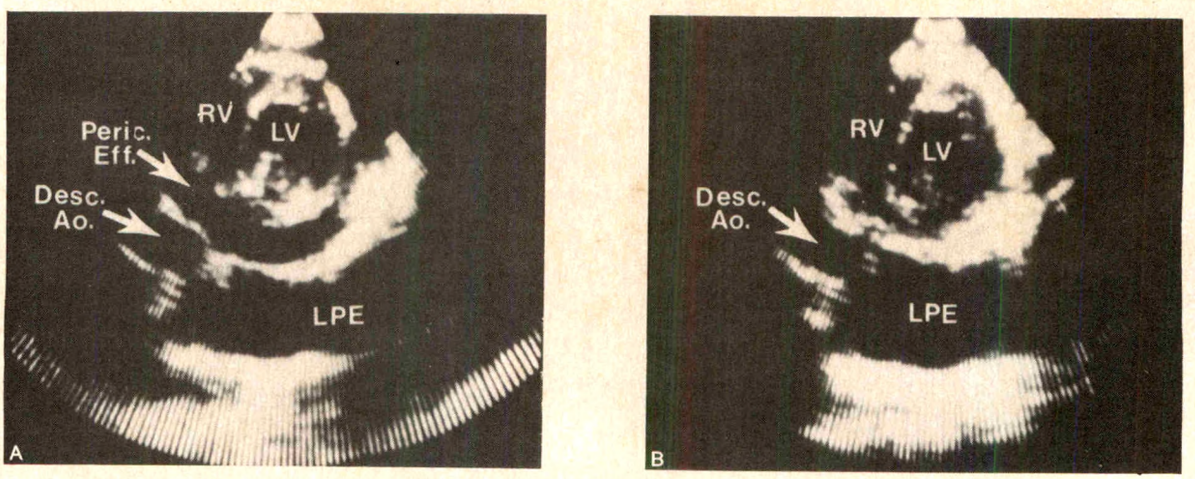


FIGURE 4. Parasternal short axis views in a patient with both a posterior pericardial (Peric. Eff.) and left pleural effusion (LPE). **A**, the effusions appear as echo-free spaces both anterior and posterior and lateral to the descending thoracic aorta (Desc. Ao.). There is a separation between the descending aorta and left ventricular (LV) posterior wall. **B**, after pericardiocentesis there is disappearance of the anterior echo-free space; the left pleural effusion remains. RV = right ventricle.

peared to be most useful for localizing the effusion. In the parasternal short axis view, pericardial effusion appeared as an echo-free space interposed between the descending thoracic aorta and the left ventricular posterior wall. A pleural effusion was visualized as an echo-free space posterior and lateral to the descending thoracic aorta. Combined pericardial and pleural effusions were visualized as echo-free spaces both anterior to and posterior and lateral to the descending thoracic aorta. The spatial relation between the descending thoracic aorta and left ventricular posterior wall that exists in the absence of any type of effusion was altered in the presence of a pericardial effusion. The descending thoracic aorta was not seen in its normal position adjacent to the left ventricular wall, but was separated because of effusion's effect of pushing the heart anteriorly or the descending thoracic aorta posteriorly.

Both pericardial and pleural effusions accumulate initially in the most dependent portion of the pericardial and pleural cavities; therefore, a posterior echo-free space is usually present posteriorly before an anterior echo-free space in a supine echocardiographic study.[4,6,22] Gravity maximizes the space between the descending thoracic aorta and both the pericardial and pleural interfaces. Thus, early detection of a posterior pericardial effusion with the M mode technique would also apply to two dimensional echocardiography. This would suggest that the echocardiographic patterns described should be sensitive and should occur even with small effusions.

Clinical implications: The patients who formed the basis of our study were selected as patients who demonstrated a distinct two dimensional echocardiographic pattern and who had anatomic confirmation of their echocardiographic findings. Therefore, by design, most of our patients had large effusions. The determination of the exact sensitivity and specificity of these findings awaits additional prospective study. However, we believe that the intimate relation of the descending thoracic aorta to the left ventricular posterior wall, pericardium and pleura is a valuable landmark in detecting and differentiating pericardial from pleural effusions.

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Histologic and Ultrastructural Features of Normal Human Parietal Pericardium

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Morphologic studies of normal anterior parietal pericardium from seven patients revealed this tissue to be composed of three layers: (1) the serosa, consisting of a surface layer of mesothelial cells and a narrow submesothelial space, (2) the fibrosa, containing variously oriented layers of collagen fibrils and small elastic fibers, and (3) the epipericardial connective tissue layer, containing mainly large coarse bundles of collagen and forming part of the pericardiosternal ligament. Scanning electron microscopic examination is most useful for study of the surface features of pericardial mesothelial cells, which have single cilia and are covered with microvilli. The latter bear friction and increase the surface area for fluid transport. Junctional complexes between adjacent mesothelial cells consist of desmosomes, which reinforce intercellular adhesion and zonulae occludentes, which form permeability barriers. Actin-like filaments (50 Å in diameter) are present in microvilli and in immediately subjacent regions of the cells; these filaments mediate changes in cell shape. Intermediate filaments (100 Å in diameter) are associated with desmosomes and form bundles in the perinuclear regions; these filaments provide structural support to the cytoplasm.

Although pericardial disease constitutes an important aspect of cardiovascular pathology, little information is available on the fine structure of the pericardium in health or in disease. No scanning electron microscopic studies of pericardium have been reported, and the only transmission electron microscopic observations made on this tissue[1–5] have been essentially limited to the mesothelial cell layer. A new stimulus for studying the ultrastructural features of the pericardium has been provided by the clinical use of parietal pericardium for bioprosthetic heart valves and for patches to repair various cardiovascular lesions. Detailed knowledge of the morphologic characteristics of normal pericardium is essential to evaluate the long-term durability and usefulness of these products. This study describes histologic and transmission and scanning electron microscopic observations made on normal human parietal pericardium.

Methods

Patients: Morphologic studies were made of parietal pericardium from seven patients, six male and one female, ranging in age from 10 to 69 years (average 47), who underwent cardiac operations in the National Heart, Lung, and Blood Institute. None of the patients had a history of pericarditis. In each patient the pericardial cavity at operation contained normal amounts of fluid and the pericardium was grossly and histologically normal, with no thickening or inflammation. Small pieces of pericardium were removed from the anterior (ventral) portion of the pericardial sac, pinned on to a corkboard at their in situ dimensions, with the serosal surface up, and placed in a solution of 3 percent glutaraldehyde in 0.1 *M* phosphate buffer, pH 7.2. The tissues were then washed with several changes of 5 percent sucrose in 0.1 *M* phosphate buffer, pH 7.2, and cut into smaller pieces for histologic and ultrastructural study.

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Histologic and electron microscopic preparation: For histologic study, tissues were embedded in paraffin and in glycolmethacrylate plastic medium. Paraffin sections were stained with hematoxylin-eosin and alkaline toluidine blue. For scanning electron microscopy, tissues were dehydrated, critical point-dried, coated with gold-palladium and examined at an accelerating voltage of 20 kV. For transmission electron microscopy, tissues were dehydrated with a graded series of ethanols and propylene oxide and embedded in Maraglas®[6] with use of flat embedding molds to obtain proper orientation of the tissue. Ultrathin sections were stained with uranyl acetate and lead citrate. Selected sections were stained according to the method of Kajikawa et al.[7] for the selective demonstration of elastic fibers.

Results

Histology

The parietal pericardium (Fig. 1, A to C) was composed of three layers: the serosa, the fibrosa, and an outer layer of epipericardial connective tissue. The serosa consisted of a surface layer of mesothelial cells and of a narrow submesothelial space (about 2 μ in width) that separated the mesothelial cells from the fibrosa, the underlying layer. The population density of mesothelial cells varied from one area to another, even when the normal dimensions of the tissue were maintained during fixation; under these conditions, the mesothelial cells appeared greatly flattened and showed mild bulging in the region of the nuclei. Microvilli were demonstrable by light microscopic study of sections of plastic-embedded tissue (Fig. 1D). When the pericardium was dropped into the fixative without maintaining its in vivo dimensions, the mesothelial cells appeared thicker and less flattened, and their nuclei showed more prominent bulging. The fibrosa was composed of connective tissue cells, small vessels, compactly arranged collagen (Fig. 1A) and small, inconspicuous elastic fibers (Fig. 1B). The epipericardial connective tissue layer contained collagenous and elastic fibers, adipose tissue cells, neural elements and blood vessels. A few mast cells, lymphocytes and histiocytes were encountered in this layer and in the fibrosa.

Several layers of collagenous bundles were recognizable in the fibrosa (Fig. 1A). The bundles immediately subjacent to the mesothelial cells appeared oriented along the cepha-

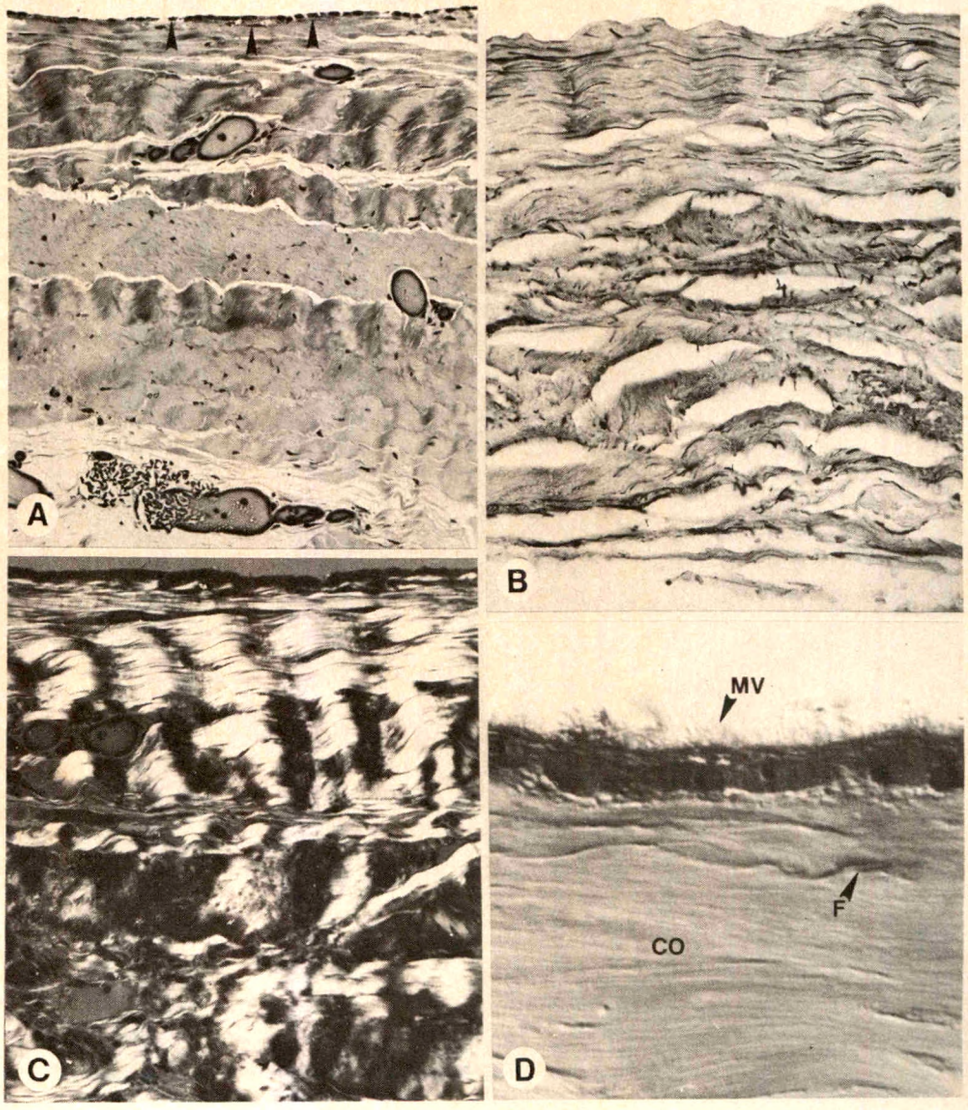


FIGURE 1. Histology of parietal pericardium. **A**, section through entire thickness of parietal pericardium showing the mesothelial cell layer (**arrowheads**); several layers of collagen fibers; small thin-walled vessels, and a few scattered connective tissue cells. One micron-thick plastic section, alkaline toluidine blue stain. **B**, section oriented as in **A**, but stained by the elastica-von Gieson method to demonstrate presence of small elastic fibers (shown in **black**) throughout the thickness of the pericardium. **C**, polarized light micrograph of area similar to that in **A**, showing birefringence of oriented collagen fibers that follow a wavy course. **D**, high magnification view of mesothelial cells, showing surface microvilli (MV) and dense collagen (CO) in submesothelial layer. Note elongated fibroblast-like cell (F) between collagen fibers. One micron-thick plastic section examined using Nomarski differential interference contrast optics. (Magnifications: **A** and **B**, ×160; **C**, ×250; **D**, ×1,600, all reduced by 27 percent.)

lad-caudad axis. Deeper layers showed more of a weaving pattern, with collagen bundles running in various directions. This arrangement was examined in detail by using a polarized light microscope to demonstrate the birefringence of collagen (Fig. 1C). Elastic fibers were usually small (less than 2 μ in diameter), and frequently were oriented perpendicular to the collagen bundles. The elastic fibers immediately subjacent to the mesothelium were smaller than were those in deeper areas of the fibrosa. Embedded in the connective tissue of the fibrosa were slender, greatly elongated connective tissue cells with long, thin nuclei and scanty cytoplasm. Some of these cells had fine cytoplasmic processes that extended parallel to the collagen bundles. Vessels penetrated, usually in an oblique manner, from the epipericardial layer toward the serosa, and frequently extended up to a distance of only 8 μ from the surface. Some vascular channels were dilated and thin-walled and probably represented lymphatics. Some of the collagen bundles in the epipericardial connective tissue layer were very coarse and provided connections between the pericardium and the anterior mediastinum (pericardiosternal ligament).

Scanning Electron Microscopy

On examination at low magnification, the serosal surfac of the pericardium appeared completely covered by meso thelial cells, which were polygonal in outline and did not sho a pattern of preferential orientation. The surfaces of th mesothelial cells contained numerous microvilli that measure up to 3 μ in length and 0.1 μ in width. In many areas, the mi crovilli completely covered the surfaces of the cells (Fig. 2A) In other areas, the microvilli tended to be concentrated in th central portions of the cells, leaving relatively smooth area in their peripheral portions. Occasionally, microvilli wer concentrated in peripheral regions of some cells, the centra areas of which appeared smooth (Fig. 2B). Other cells hac either knob-like protrusions or cup-like depressions in th central areas of their surfaces. Single cilia, which were thicke and considerably longer than microvilli, were also found i some cells. Observations by transmission electron microscop confirmed that these structures were cilia.

Areas of intercellular junctions were visualized as discret narrow ridges (Fig. 3A). No intercellular spaces were presen

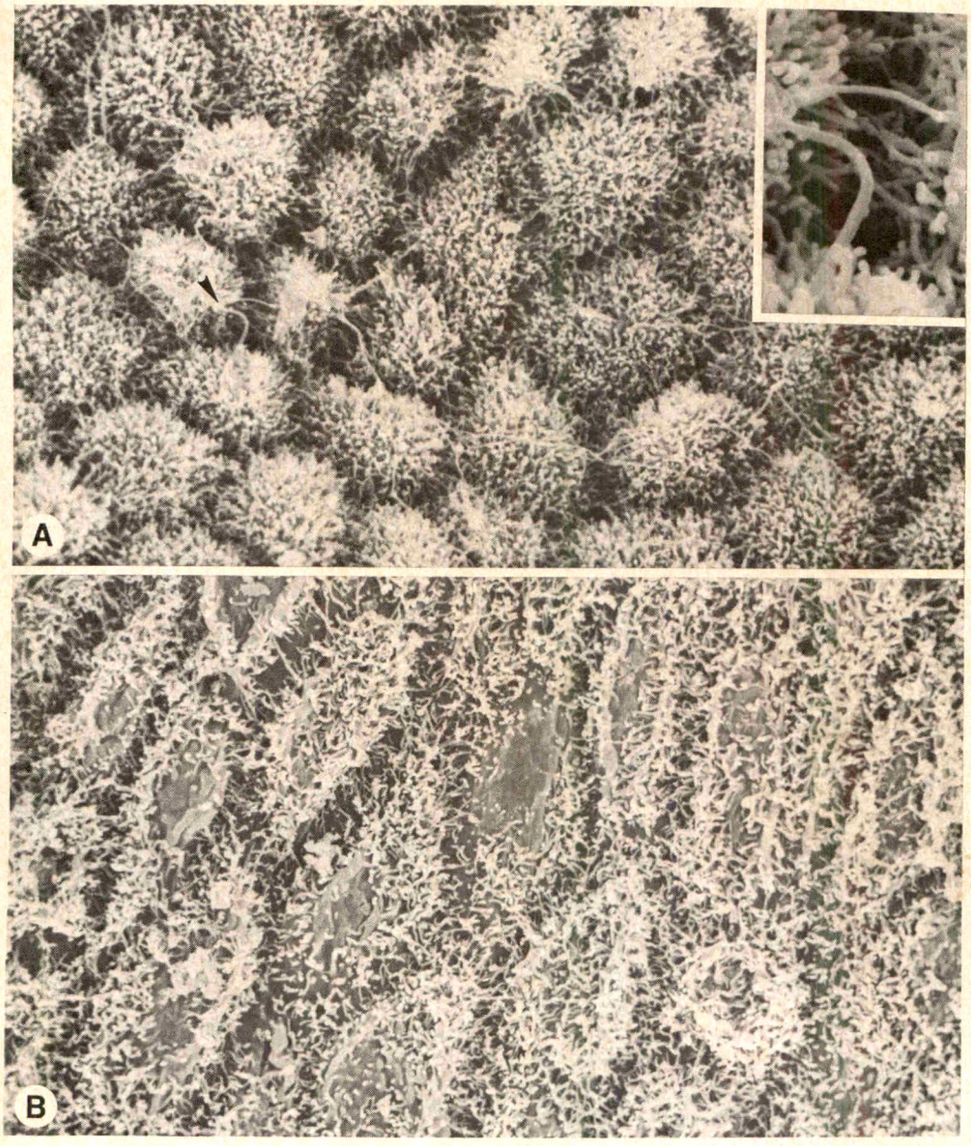


FIGURE 2. Scanning electron micrographs of human parietal pericardium. **A**, view of area in which the serosal surfaces of the mesothelial cells are completely covered by microvilli. Cilia (**arrowhead**), which are thicker and considerably longer than microvilli, are also distinguishable. **Inset** shows higher magnification view of cilium indicated by **arrowhead. B,** view of area in which microvilli tend to form rings near peripheral portions of the cells, leaving smooth central portions. (Magnifications: **A**, ×3,800 (**inset,** ×10,000); **B**, ×3,400, all reduced by 27 percent.)

between adjacent mesothelial cells. In areas from which the mesothelial cells had been accidentally detached during the course of specimen preparation, the serosal surface was composed of bundles of collagen fibrils (Fig. 3B). These bundles had a wavy appearance and were covered by a layer of material without discernible substructure. This layer (Fig. 3C) corresponded to the basal lamina of the mesothelial cells. Individual collagen fibrils were clearly evident within these superficial bundles only when the serosal surface had been more strongly abraded (Fig. 3, D and E).

The mediastinal surface of parietal pericardium (*Fig. 3F*) contained large collagen bundles that coursed in various directions, measured up to 15 μ in diameter and projected above the surface. These bundles, which were much larger than those subjacent to the serosal surface, imparted a characteristic appearance to the mediastinal surface. Subjacent to these bundles was a more homogeneous layer of collagen bundles, which were smaller and more tightly packed. Individual fibrils were evident within these bundles only when they had been disrupted.

Transmission Electron Microscopy

The mesothelial cells (*Fig. 4, A to D*) formed a continuous monolayer, but in some areas the overlap between adjacent cells was considerable, even to the extent that stacked profiles of three cells could be found (Fig. 4C). A distinct glycocalyx or fuzzy coating (less than 100 Å in thickness) was evident on the external leaflet of the plasma membrane in the luminal or serosal surface (Fig. 4B). Microvilli measured 0.1 μ in diameter and contained fine filaments that were oriented longitudinally and measured 50 Å in diameter (Fig. 4B). These filaments were also present, in a less organized arrangement, in areas of cytoplasm immediately subjacent to the microvilli (Fig. 5, A to C). Cilia were encountered occasionally and were composed of rootlets, a basal body and a core of regularly arranged microtubules (Fig. 4D). Pinocytotic vesicles were present only in small numbers along the luminal surfaces. The lateral surfaces of the mesothelial cells were closely interdigitated and apposed over most of their course (Fig. 4C, 5, B and C and 6, A and B). Specialized intercellular junctional

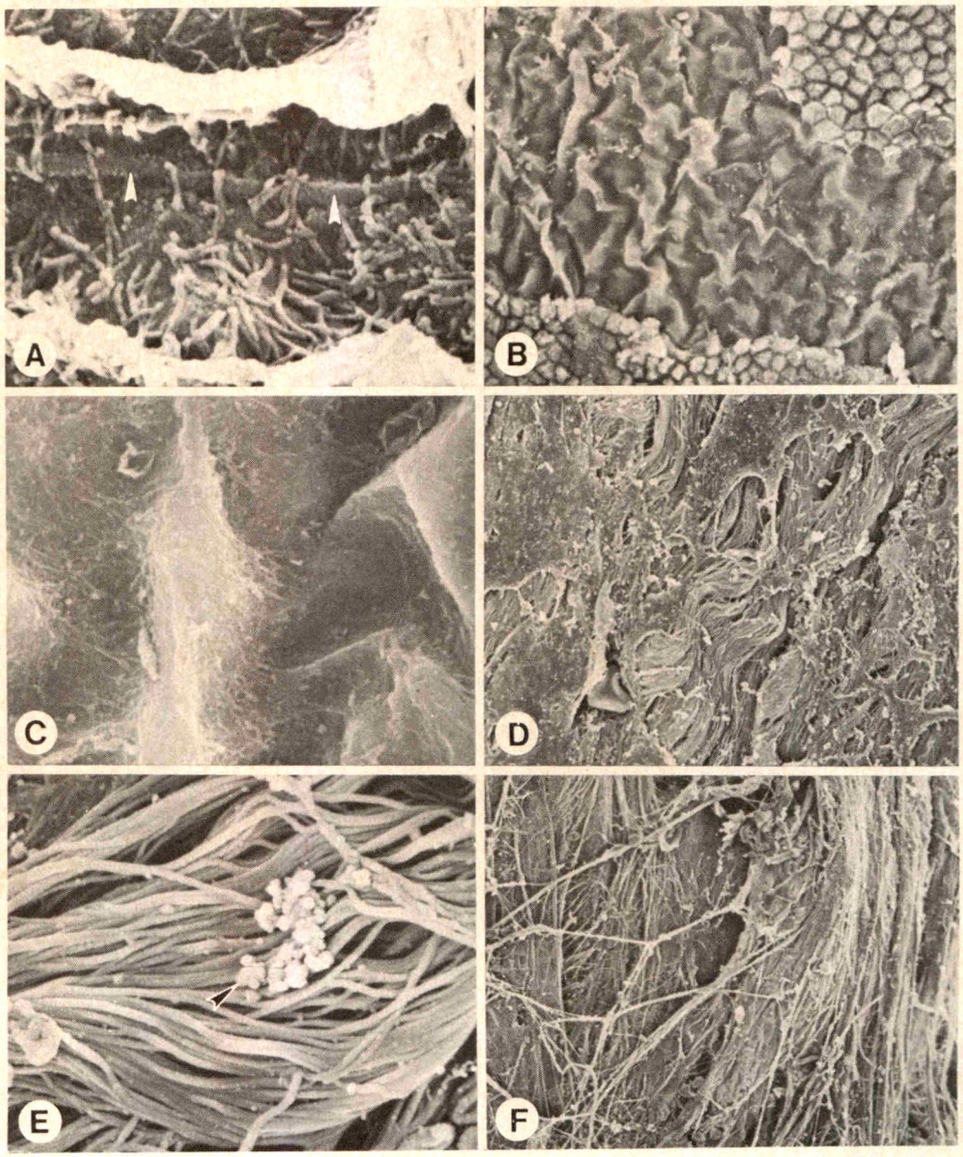


FIGURE 3. Scanning electron micrographs of human parietal pericardium. **A**, intercellular junction appears as a slightly elevated ridge (**arrowheads**). **B**, area of partial denudation of mesothelial cell layer. Some mesothelial cells remain (**bottom and upper right**). Surface of denuded area has a wavy configuration that reflects arrangement of underlying collagen. **C**, high magnification view of area similar to that shown in **B**. The surface is relatively smooth; it is composed of basal laminar material, and collagen fibrils are not evident. **D**, area of surface from which the mesothelial cells have been completely denuded and the basal lamina has been partially removed, exposing underlying bundles of collagen fibrils. **E**, high magnification view of center of area shown in **D**. Collagen fibrils are seen as discrete units, together with some cellular debris. **F**, low magnification view showing large coarse collagenous bundles in the pericardial surface that faces the sternum. (Magnifications: **A**, ×10,000; **B**, ×300; **C**, ×3,000; **D**, ×1,000; **E**, ×10,000; **F**, ×100, all reduced by 27 percent.)

structures along these lateral surfaces were few in number and consisted of zonulae occludentes (Fig. 5, B and C and 6A) and desmosomes (Fig. 5D and 6A). The apposed lateral plasma membranes were separated by an intercellular space of about 200 Å in width; however, in areas of zonulae occludentes, the apposed outer leaflets of the two plasma membranes appeared as single lines. The space between adjacent cells also showed focal dilatations of up to 1 μ in width. Some of these dilatations contained microvilli (Fig. 6A); others were filled by basal lamina material (Fig. 6B). Zonulae occludentes measured up to 0.4 μ in length and typically were present at the points where the areas of apposition terminated at the luminal surfaces (Fig. 5B and C). Zonulae occludentes were less commonly present near the abluminal surface. Desmosomes were small (up to 0.5 μ in length) and were the sites of insertion of bundles of cytoplasmic filaments (Fig. 5D and 6A). These filaments measured 100 Å in diameter; therefore, they were larger than those associated with the microvilli. In some cells, the 100 Å filaments formed bundles that coursed around the nuclei (Fig. 6C). In addition to microvilli, the luminal surfaces of the mesothelial cells showed irregularly shaped invaginations that extended for variable distances into their cytoplasm (Fi 5A).

The basal surfaces of the mesothelial cells showed rel tively minor folds and moderate numbers of pinocytotic ve icles; however, they did not exhibit cytoplasmic processes th projected deeply into the underlying connective tissue. some areas, the basal surface had a clear, well defined bas lamina, that measured up to 500 Å in width and was subd vided into a lamina densa and a lamina clara (Fig. 4C). Hov ever, in most areas the basal lamina material extende without any zones of discontinuity, from the basal surfac of the cells through the submesothelial space and into th uppermost layer of collagen fibrils in the fibrosa (Fig. 6B an 7A). The extent of irregularity of the basal surfaces of th mesothelial cells appeared to be related to the degree of fla tening and elongation of the cytoplasm. Tubular invaginatio of cytoplasm were also present along the basal surfaces of th mesothelial cells; some of these invaginations contained bas laminar material (Fig. 5D). Hemidesmosomes, anchoring f brils or other structures that can attach cells to the underlyir connective tissue were not present in parietal pericardium

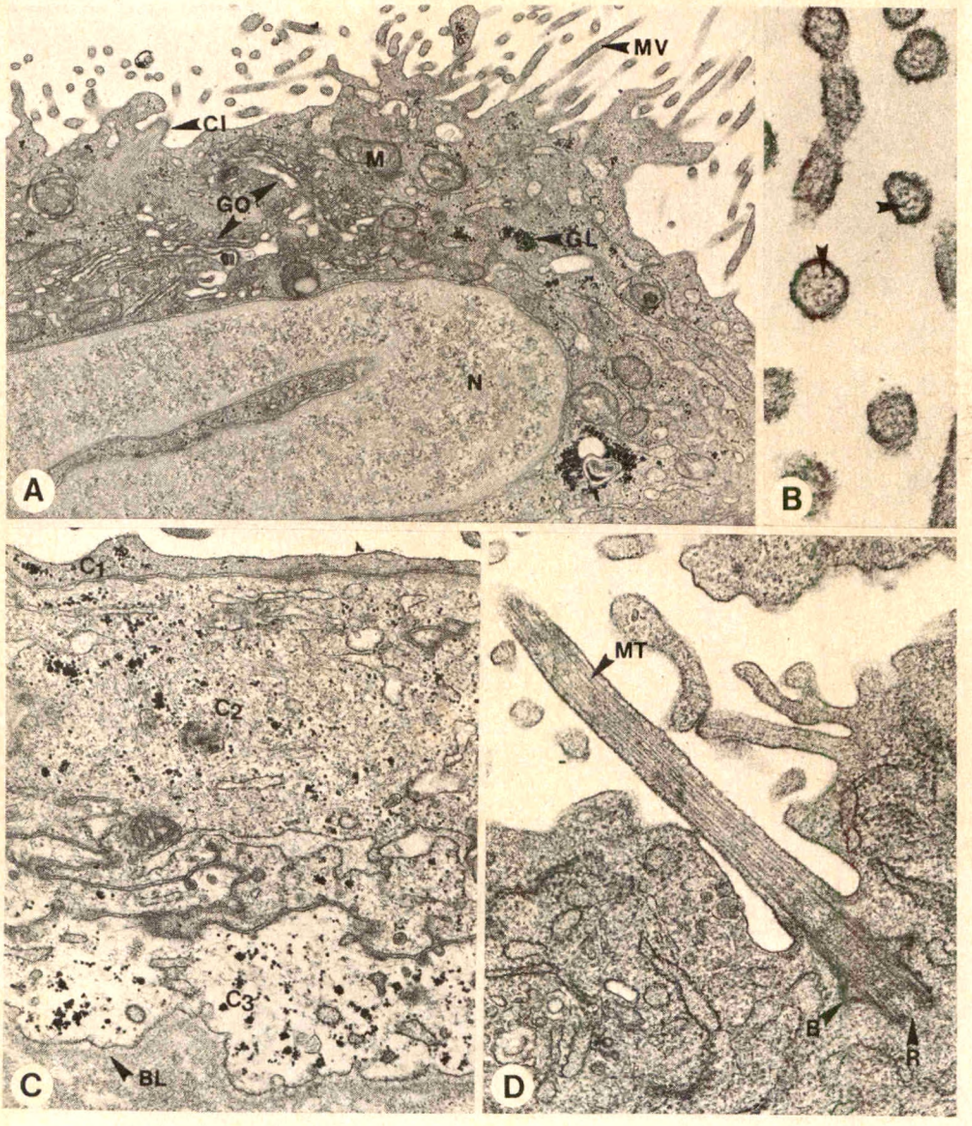


FIGURE 4. Transmission electro micrographs of the surfaces pericardial mesothelial cells. **A** perinuclear region of mesotheli cell, showing nucleus (N), prom nent Golgi complexes (GO), glyc gen granules (GL), mitochondria (M microvilli (MV) and part of the bas of a cilium (CI). **B**, cross sections microvilli showing the trilamina membrane, the fuzzy coat on th surface, and the core filament (**arrowheads**). **C**, area of overlap three cells. At the top, a very thir flattened cell with dense cytoplasr is present (C_1). Subjacent to thi cell, there is a second cell with les dense cytoplasm (C_2). A third ce (C_3) with clear cytoplasm is found the bottom, overlying a discret basal lamina (BL). **D**, longitudina section through a cilium, showing it basal body (B), rootlets (R) and th microtubules (MT) in its main seg ment. Note the microvilli and th cisterns of endoplasmic reticulun adjacent to the cilium. (Magnifica tions: **A**, ×20,400; **B**, ×97,000; **C** ×27,000; **D**, ×38,000, all reduce by 27 percent.)

The cytoplasm of the mesothelial cells (Figs. 4, A and C, 6, B and C) contained: small numbers of mitochondria and lysosomes; large, well developed Golgi complexes composed of stacks of parallel cisterns; moderate numbers of multivesicular bodies; cytoplasmic filaments of two types: actin-like (40 to 75 Å in diameter) and cytoskeletal (100 Å in diameter) as described earlier; a few microtubules; and variable numbers of glycogen granules, lipid droplets and cisterns of rough-surfaced endoplasmic reticulum. Indentations and folds were present in the nuclear membranes of some cells. The nuclei contained a moderately prominent nucleolus. In one of the seven patients, the spaces between the inner and outer nuclear membranes contained small clusters of vesicles (Fig. 6C).

The cytoplasmic density of mesothelial cells varied considerably (Fig. 4C). Some cells appeared dense, primarily because of their high content of free ribosomes and cisterns of endoplasmic reticulum; other cells had few of these components, and for this reason they appeared much more electron-lucent. These differences appeared to represent a continuum of variations rather than two or more distinct cell types. In addition, some cells had clear areas of cytoplasm associated with apparent displacement of organelles to one side of the cell. These areas of cytoplasm showed poor tissue preservation and were regarded as being sites of fixation artifacts.

The fibrosa contained collagen (Fig. 7A), elastic fibers (Fig. 7B) and flattened cells (Fig. 7C), which in many ways resembled the veil cells described in arterial adventitia.[8] These cells contained few organelles and had long cytoplasmic processes, in which a few mitochondria, occasional cisterns of rough-surfaced endoplasmic reticulum and sparse, actin-like and cytoskeletal filaments were present.

The collagen fibrils showed their usual periodic banding. Their diameter ranged from 500 to 1,500 Å and averaged 850 Å. They were arranged parallel to the surface and they formed tightly packed bundles or sheets that were oriented in different directions. The arrangement of the collagen fibrils was very compact, and in some areas the direction of adjacent bundles or sheets of collagen changed quite sharply (Fig. 7A). In most areas, the amount of interfibrillary material was small and no spicules (that is, such as those present[9] in arterial walls) of proteoglycan material were seen. In most areas, the collagen

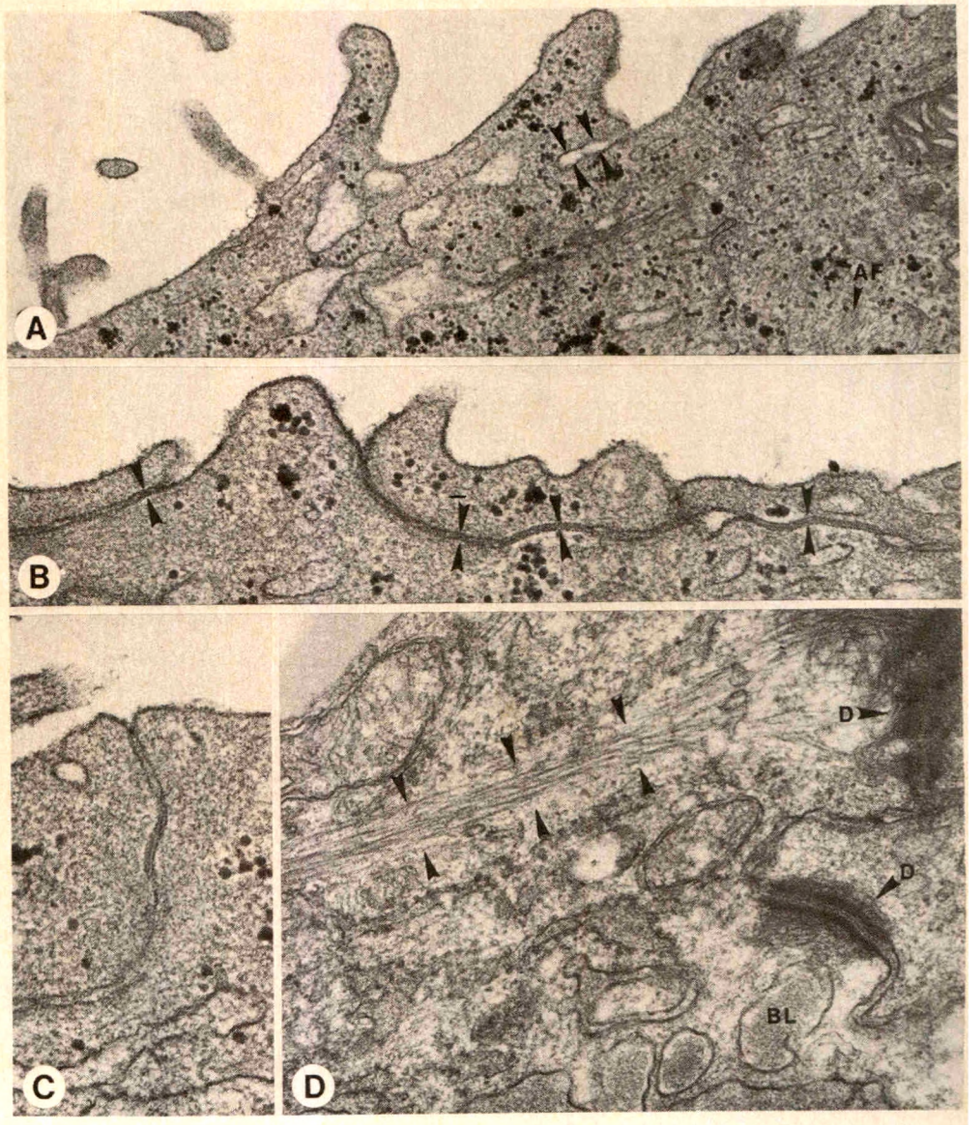


FIGURE 5. Surface features and junctional complexes of pericardial mesothelial cells. **A**, irregular surface folds are associated with invaginations (**arrowheads**) and differ clearly from microvilli (**left**). Actin-like cytoplasmic filaments (AF) are present in the cytoplasm. **B**, zonulae occludentes (**arrowheads**) form permeability seal between adjacent mesothelial cells. **C**, high magnification view of zonula occludens similar to those shown in **B**. Note transport vesicle at left of junction. **D**, typical desmosomes (D) are associated with bundles of intermediate (100 Å in diameter) filaments (**arrowheads**). Cytoplasmic invaginations containing basal lamina material (BL) are present along the basal surface of the cell. (Magnifications: **A**, ×41,000; **B**, ×73,000; **C**, ×88,400; **D**, ×60,300, all reduced by 27 percent.)

fibrils were intimately associated with a network of delicately fibrillar material of undetermined nature.

Elastic fibers (*Fig. 7, B and C*) ranged from 0.3 to 0.7 μ in diameter and showed their two usual components: the centrally located elastin material, which was selectively stained black by the Kajikawa method, and the peripherally located microfibrils (130 to 150 Å in diameter). Small bundles of microfibrils were occasionally found between collagen fibrils but without being associated with elastin material.

Discussion

The observations in this study demonstrate the complexity of the organization of the various structural components of human parietal pericardium and illustrate the range of adaptations that this tissue has developed in order to perform its functions. These adaptations were evident in the mesothelial cell layer (serosa) as well as in the underlying connective tissue layer (fibrosa).

Mesothelial Cells

Microvilli and cilia: The most striking morphologic feature of pericardial mesothelial cells was the presence of microvilli and cilia on the serosal or luminal surfaces. Microvilli were extremely numerous and covered most of the luminal surface area. These microvilli were more numerous than those in peritoneal mesothelial cells[10–13] and resembled those in pleural mesothelial cells.[14,15] Microvilli are also present in mesotheliomas.[16,17] We attribute at least two functions to microvilli: (1) They provide pericardium with specialized friction-bearing surfaces, and (2) they increase the cell surface area available for fluid transport.

The cilia found in pericardial mesothelial cells differed from microvilli in size and substructure. Cilia are capable of motility, often in the form of a sweeping motion. The motility of cilia is mediated through the side arms on their microtubules.[18] In contrast to these

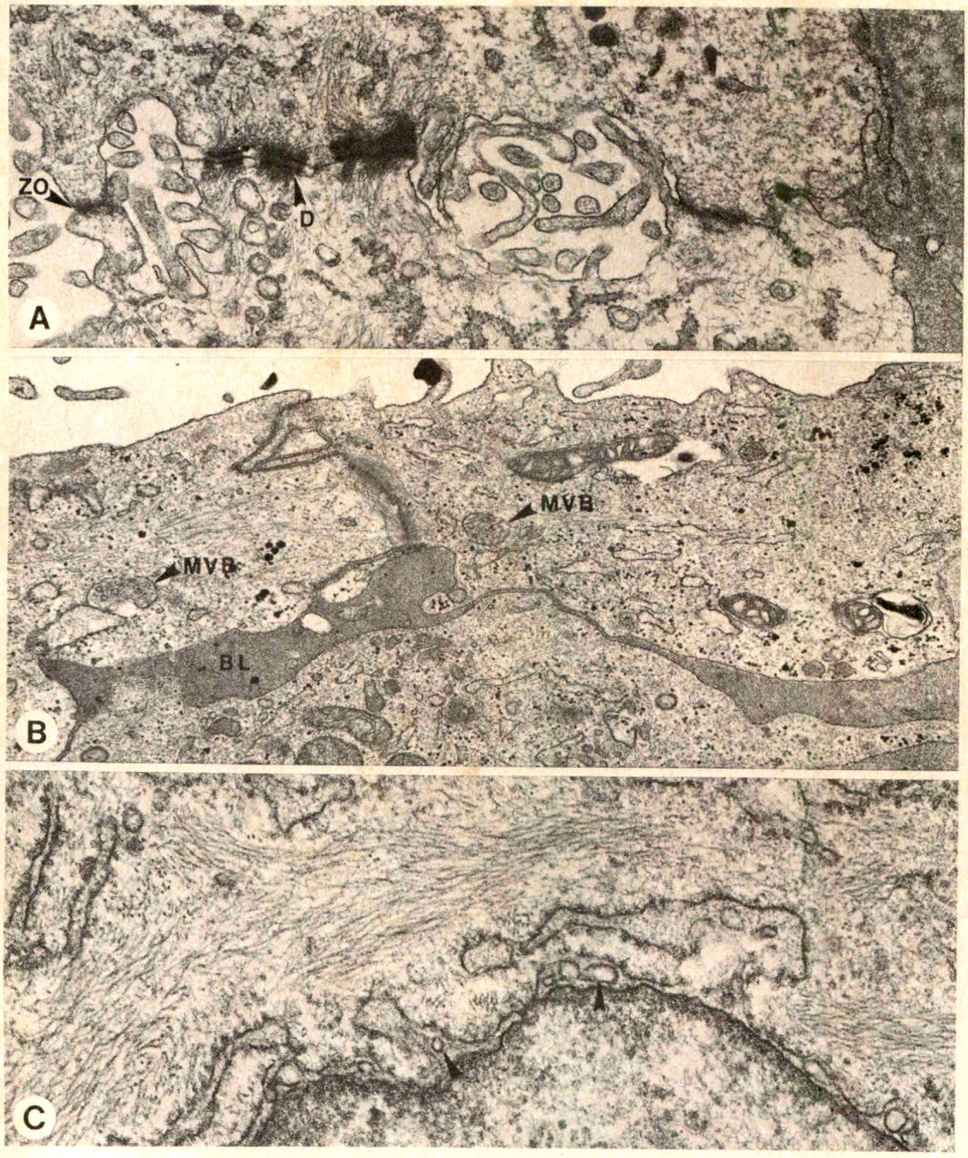


FIGURE 6. Junctions and cytoplasmic filaments of pericardial mesothelial cells. **A**, junction between two cells extends from luminal surface (**left**) to basal surface (**right**). A zonula occludens (ZO) is located at the luminal end, and several desmosomes (D) associated with 100 Å filaments are found in adjacent regions of the junction. Note presence of microvilli in two areas of widening of the intercellular space. **B**, intercellular space in area of overlap between adjacent cells is filled by basal lamina material (BL). Note multivesicular bodies (MVB) in two of the cells. **C**, bundles of 100 Å filaments course in vicinity of nucleus of mesothelial cell. Small vesicles (**arrowheads**) are located in the space between the inner and outer nuclear membranes. (Magnifications: **A**, ×31,900; **B**, ×24,300; **C**, ×74,400, all reduced by 27 percent.)

features, microvilli lack a basal body and microtubules and contain only a core of longitudinally oriented microfilaments. Microvilli also undergo changes in shape that are presumably mediated by their core filaments. These filaments insert into the tips of the microvilli and constitute a network that extends below their base. In intestinal epithelial cells the core filaments associated with microvilli have been shown to be composed of actin[19–21] and to bind heavy meromyosin (a property typical of actin filaments) with specific patterns of orientation of the resulting "arrowhead" complexes.[19,20] The passive changes in shape pericardial mesothelial cells undergo with cardiac systole and diastole are not known. Nevertheless, it is clear that these cells possess the subcellular components needed to alter actively the configuration of their luminal surfaces.

Transport systems: The luminal and basal surfaces of pericardial mesothelial cells had irregularly shaped invaginations of the plasma membranes as well as multivesicular bodies and coated and uncoated vesicles. These structures are known to function in transport of fluid and protein materials. It is reasonable to postulate that the two types of transport systems existing in other cells[22] are also present in pericardial mesothelium: transport through the intercellular spaces and transport across the cytoplasm by means of vesicles. The latter would form by invagination of the plasma membrane at one surface, pinch off, move across the cytoplasm, fuse with the plasma membrane at the opposite surface of the cell, and then discharge their content into the extracellular space. The relative importance of these two mechanisms in pericardial mesothelial cells is unknown. Studies of pericardial transport functions[23–26] have shown that relatively small molecules can be removed from the pericardial cavity, presumably by way of subepicardial capillaries, and that larger molecules and discrete particles (colloidal gold, colloidal carbon) are removed extremely slowly. Entry into lymphatics from the pericardial cavity seems to occur with the greatest difficulty and very slowly.[23] The findings of these functional studies, indicating very slow removal of macromolecules from the pericardial cavity, are in accord with the observations of Kluge and Hovig[3,4] and of the present study, in which zonulae occludentes were demonstrated in the intercellular junctions connecting pericardial mesothelial cells. Such junctions, which typically were present near the two terminations of the zone of cell to cell apposition at the basal lamina and at

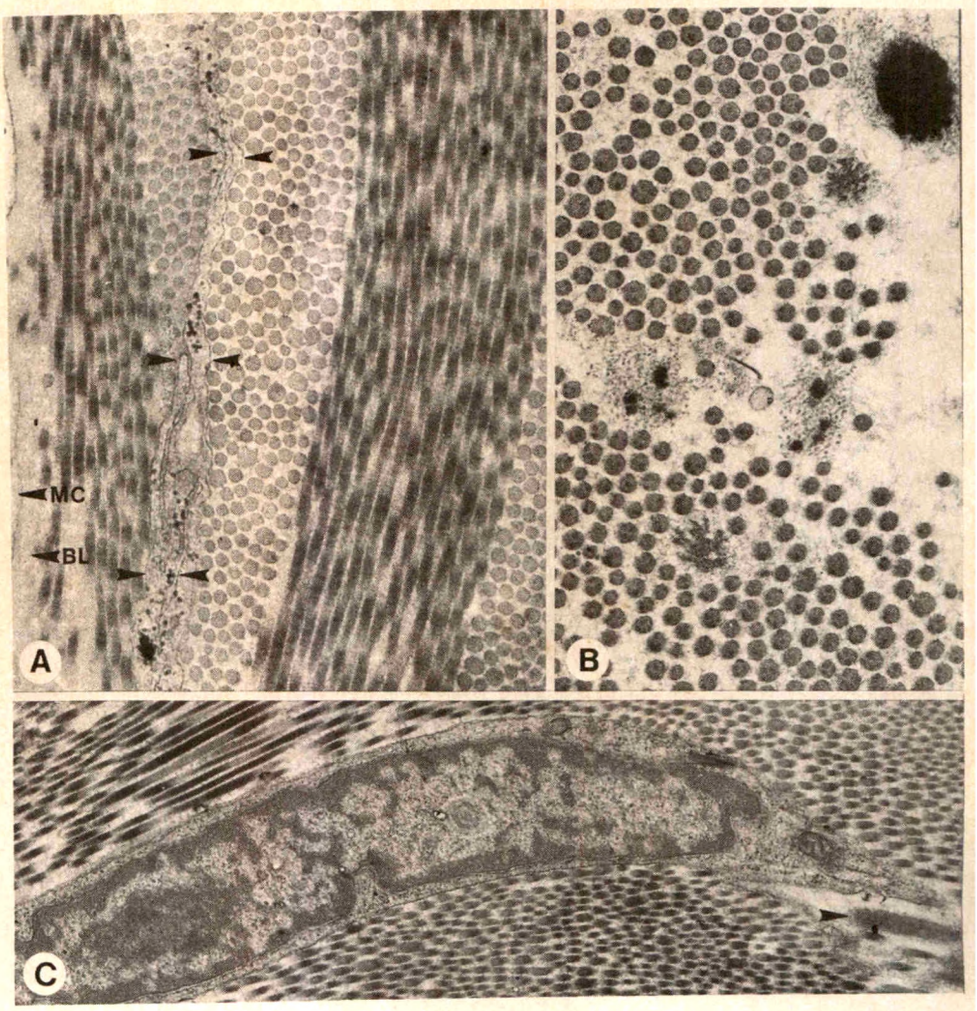


FIGURE 7. Transmission electron micrographs of pericardial connective tissue. **A**, section through submesothelial area showing the basal surface of a mesothelial cell (MC), the basal lamina (BL), several layers of variously oriented collagen fibrils, and part of the cytoplasm (**arrowheads**) of a greatly elongated fibroblast-like cell. **B**, section stained according to Kajikawa et al.[7] for the demonstration of elastic fibers. The elastin cores are darkly stained, particularly in the elastic fiber (**upper right**); other elastic fibers (**center** and **bottom**) contain abundant microfibrils and small elastin cores. **C**, nuclear region of elongated fibroblast-like cell in pericardial tunica fibrosa. A small elastic fiber (**arrowhead**) is shown (**lower right**). (Magnifications: **A**, ×32,000; **B**, ×43,250; **C**, ×20,300, all reduced by 27 percent.)

the luminal border, are known to constitute barriers sharply limiting the passage of macromolecules that could cross the mesothelial layer by the intercellular route. In contrast to this, the desmosomes (the other type of specialized structures present in pericardial mesothelial cells) provide points of reinforcement of intercellular adhesion but do not represent an additional permeability barrier. The number of cytoplasmic vesicles was relatively small, indicating that transport through parietal pericardial mesothelial cells by the transcellular route is limited.

Internal structural support system: The presence of large areas of overlap and interdigitation between adjacent cells would indicate that the mesothelial layer has the capacity to accommodate to changes in shape of the cells, and particularly to stretching. The bundles of filaments measuring 100 Å in diameter (intermediate filaments), in the cytoplasm of mesothelial cells are considered to constitute a cytoskeleton that serves to stabilize cell shape. These filaments are biochemically and morphologically different from the actin and myosin types of filaments.[27] Thus, the cytoplasm of mesothelial cells does have a system of internal structural support.

Function of reticulum: The functions of the Golgi complexes and the cisterns of rough-surfaced endoplasmic reticulum that were very abundant in some cells are not known. Similarly, the significance of the "clear" cells observed by us and by Kluge and Hovig[3,4] is unknown. We believe that these variations represent differences in the age of the cells. Perhaps the cells that contain more abundant endoplasmic reticulum are younger and more active, or are growing cells that are replacing senescent cells. Cells rich in endoplasmic reticulum had less abundant microvilli. An important function of the reticulum may be the elaboration of plasma membrane and filamentous components of the microvilli.

It remains to be determined whether pericardial mesothelial cells can respond to inflammation by undergoing cellular contraction and junctional separation, with a resulting increase in permeability and leakage of fluid from the interstitial spaces in the surface of the heart into the pericardial cavity. This mechanism would be analogous to that shown to occur during endothelial cell injury in inflammation.[21]

Connective Tissue Components

Pericardial basal lamina: The configuration of the pericardial basal lamina was variable. In some areas the basal lamina material was evident as a discrete layer, whereas in others it blended directly with the material surrounding the most superficial collagen fibrils in the tunica fibrosa. These findings, and the lack of hemidesmosomes or other structural devices reinforcing the attachment of the basal surfaces of the cells to the underlying connective tissue, are in accord with the observations in this study that the attachment of pericardial mesothelial cells to the submesothelial layer is very fragile. Indeed, mesothelial cells can be easily removed from unfixed specimens by contact with fingers or surgical instruments. The continuity of the basa lamina material with the interfibrillary material in th collagen layer was also demonstrated in the scannin electron micrographs of denuded areas of parietal per icardium. In these areas, the surface layer appeare smooth, and collagen fibrils were evident as discret units only when the surface layer was traumatized to th extent of removing the basal lamina material.

Collagen fibrils in fibrosa: The layers of collage fibrils in the fibrosa varied in orientation, thus allowin some degree of multidirectional stretch to take place Stretch also appeared to be permitted by the wavy ar rangement of collagen fibrils within a given bundle o layer, so that mild tension could lead to elongatio mediated by straightening of the wavy fibrils. Never theless, it would appear that very little stretch is pos sible after the collagen has been straightened out, be cause collagen fibrils are known to be very inextensi ble.[28,29] This feature seems to be the reason that smal increments in the amount of pericardial fluid at firs cause little or no increase in intrapericardial pressure and then a small additional amount of fluid can lead t a large increase in intrapericardial pressure.[26]

Relation of age to pericardial structure: Althougl the number of patients in our study was too limited t permit investigation of the ultrastructural aspects o this problem, a relation between age and connectiv tissue morphology has been observed in previous his tologic studies of human pericardium. In a study of 20 human pericardia, Hort and Bräun[30] demonstrate that: (1) pericardial collagen fibrils in younger fetuse are delicate and nonwavy; (2) in pericardium from olde fetuses, collagen fibrils become wavy as elastic fiber first develop; (3) the waviness of pericardial collage becomes maximal in young adulthood and decrease thereafter; and (4) as collagen becomes less wavy i older persons, elastic fibers do not decrease in numbe but the structure of pericardial connective tissue be comes progressively less organized. This study, and the work of Wallraff[31] showing that strips of pericardium from young subjects were more extensible than those from older subjects, also suggests that the waviness o collagen is a major determinant of pericardial disten sibility.

Differences between pericardial fibrosa and fibrosa of porcine valves: The fibrosa of parietal peri cardium appeared to be less rich in proteoglycans than is the spongiosa of porcine valves,[32] which is the laye most likely to undergo calcification in glutaraldehyde treated porcine valve prostheses.[33] In this regard, the pericardial fibrosa is more comparable with the fibrosa of porcine valves,[32] in which collagen is densely packed and elastic fibers are relatively few and small. Never theless, the collagen fibrils in the fibrosa of porcine valves are mainly oriented parallel to the free edge of the cusp,[28,29] whereas in pericardium they are much more multidirectional in orientation. It is not known whether these differences will be of importance with respect to the long-term function of valve bioprostheses made of parietal pericardium. Small elastic fibers are present in pericardium, as shown by previous histologic stud-

ies[30,34–36] and by the electron microscopic observations using specific ultrastructural staining methods in this study. The surface of anterior parietal pericardium that faces the sternum is extremely rough in texture, because of the large size of the collagen bundles and because these bundles have to be transected from their sternal attachments. The roughness of this surface may be a disadvantage in terms of the use of parietal pericardium for prosthetic patches or for construction of valve leaflets, because it may predispose to the trapping of blood elements and to thrombosis in the spaces between large collagenous bundles.

In conclusion, this study demonstrates some of the relations between structure and function in pericardium. The mesothelial cells have microvilli, which act as friction-bearing surfaces and increase the surface area available for fluid transport. They also have two sets of cytoplasmic filaments, one that provides structural support and one that mediates changes in cell shape. The junctions between adjacent cells reinforce intercellular adhesion and form a permeability barrier. The connective tissue permits only a limited amount of stretch, which is mediated by straightening of the wavy arrangement of bundles of collagen fibrils.

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True Left Ventricular Aneurysm and Healed Myocardial Infarction

Clinical and Necropsy Observations Including Quantification of Degrees of Coronary Arterial Narrowing

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Clinical and necropsy observations are described in 28 patients (24 men) aged 31 to 85 years (mean 62) with healed myocardial infarction and a true left ventricular aneurysm. In contrast to findings in other subsets of necropsy patients with fatal coronary heart disease, chronic congestive heart failure was frequent (22 patients); angina pectoris was infrequent (4 patients) and, when present, never severe; recurrence of acute myocardial infarction (2 patients), sudden death (2 patients) and clinically evident systemic emboli (1 patient) were infrequent; survival for more than 5 years after healing of the acute infarction was infrequent (in 3 of 21 patients with clinically diagnosed acute myocardial infarcts); and survival for longer than 1 year after aneurysmectomy was lacking (0 of 7 patients). Additionally, 23 of the 28 patients had a large heart (greater than 400 g [mean 523], 26 had dilated nonaneurysmal portions of the left ventricle, and all but 1 had a large (greater than 30 percent of the left ventricular wall) myocardial infarct. In 25 of the 28 patients, two or more of the four major epicardial coronary arteries were greater than 75 percent narrowed in cross-sectional area by atherosclerotic plaques. In 992 segments (each 5 mm long) of a major coronary artery examined in 22 patients (45 segments/patient), narrowing was greater than 75 percent in 323 segments (33 percent) and ranged from 51 to 75 percent in 419 (42 percent), from 26 to 50 percent in 210 (21 percent) and from 0 to 25 percent in 40 (4 percent). Thus, the scarred, hypertrophied and aneurysmally dilated left ventricle infrequently produces chest pain or fatal arrhythmia despite diffuse, severe coronary narrowing.

Although ventricular aneurysm is a relatively frequent consequence of acute myocardial infarction, surprisingly few clinicopathologic studies are available that include more than five patients with left ventricular aneurysm and healed myocardial infarction[1–5] (Table I). Consequently, we analyzed clinical and morphologic findings in 28 necropsy patients with healed myocardial infarction and left ventricular aneurysm (Table II), focusing on the amounts of coronary narrowing present, because precise anatomic information in this area is lacking. Also, we call attention to certain clinical features in these patients that distinguish them from other subsets of patients with coronary heart disease.

Methods

Study patients: *All 28 patients fulfilled the following criteria:* (1) presence of a left ventricular free wall (endocardium, myocardium and epicardium) convex protrusion, the wall of which consisted of dense fibrous tissue with or without an occasional "island" of myocardial fibers; (2) absence of myocardial necrosis within the wall of the left ventricular aneurysm; (3) diameter of the mouth of the left ventricular aneurysm larger than or similar to that of the aneurysm itself; (4) absence of associated noncoronary heart disease; and (5) examination of all hearts by both authors.

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TABLE I

Certain Clinical and Cardiac Necropsy Observations from 5 Previously Reported Studies in English Comprising More Than 20 Necropsy Patients With Left Ventricular Aneurysm

First author (year)	Phares (1953)	Schlichter (1954)	Abrams (1963)	Dubnow (1965)	Davis (1972)
Years covered	1916–1951	1930–1945	1956–1961	1952–1963	1946–1968
LV aneurysm defined	+[a]	+[b]	–	+[c]	–
Patients (n)	40	102	65	80	27[d]
Age (yr) range (mean)	37–85; (74)	36–85 (–)	– (68)	43–96 (68)	42–89 (59)
Male/female ratio	27:13	80:22	52:13	65:15	35:5
Pts (n) with aneurysm at site of MI	–	102 (100%)	63 (97%)	80 (100%)	–
Pts (n) with aneurysmal wall healed	–	61 (60%)	39 (60%)	"Most"	–
Pts (n) with associated noncoronary heart disease	–	27 (28%)	–	–	–
Angina pectoris	5 (13%)	–	–	–	25 (63%)
Chronic CHF	24 (60%)	71 (71%)	"Infrequent"	61[e] (75%)	35 (88%)
Clinical events compatible with systemic emboli	2[e] (5%)	36[e] (35%)	–	10[e] (13%)	2 (5%)
Clinical diagnosis of acute MI	20 (50%)	66 (65%)	45 (69%)	58 (73%)	36 (90%)
Pts (n) surviving 5 yr after acute MI	–	8/66 (12%)	33/45 (69%)	13/48 (27%)	–
Clinical diagnosis of aneurysm	–	–	4 (6%)	13 (16%)	6/27 (22%)
Modes of death					
Chronic CHF	16 (40%)	–	7 (11%)	–	5/27 (19%)
Acute MI	7 (18%)	–	32 (49%)	34 (43%)	16/27 (59%)
Sudden	6 (15%)	0	0	–	0
Rupture of aneurysm	0	0	2 (3%)	1 (1%)	1/27 (4%)
Thromboemboli	2 (5%)	–	0	7 (9%)	0
Noncardiac	7 (18%)	18 (18%)	23 (35%)	9 (11%)	5/27 (19%)
Rupture of nonaneurysmal wall	1 (3%)	0	0	0	0
Systemic hypertension	19 (48%)	69 (68%)	14 (22%)	23 (29%)	–
Diabetes mellitus	4 (10%)	23 (23%)	24 (37%)	–	–
Pts (n) with LV aneurysmectomy	0	0	0	0	4 (10%)
Heart weight increased	33 (83%)[f]	–	–	66[f] (83%)	–
Pts (n) with LV cavity dilated	–	–	–	–	–
Amount of coronary narrowing	Severe	Severe	–	Severe	Severe
Size of MI	–	Large	–	–	–
Intraaneurysmal thrombus	–	55 (54%)	9/65 (14%)	52 (65%)	12/27 (44%)
Pts (n) in whom heart illustrated	2 (5%)	3 (3%)	0	2 (3%)	0

[a] ". . .defects in the ventricular wall which demonstrate a definite bulge in the external contour of the heart, together with a thinning of the affected region"; [b] ". . .a localized outpouching of the cavity of a cardiac chamber, with or without outward bulging of the external surface"; [c] ". . . a protrusion of a localized portion of the external aspect of the ventricle accompanied by a corresponding protrusion of the ventricular cavity"; [d] Study included 40 patients with necropsies in 27. Data refers to all 40 patients unless specified. [e] minimal number; [f] heart weight >100 g above expected normal.

CHF = congestive heart failure; LV = left ventricular; MI = myocardial infarct; Pts = patients; – = no information.

The 28 patients (Table II) ranged in age from 31 to 85 years (mean 62); 13 were aged 65 years or older, and 24 were men. Chronic congestive heart failure occurred in 22 patients (79 percent), angina pectoris in 4 (14 percent) and clinical episodes compatible with systemic emboli in 1 (4 percent). A history of systemic hypertension, before the acute myocardial infarction, was present in 13 patients, and 5 had diabetes mellitus. Clear documentation of acute myocardial infarction was present in 21 patients and only 3 of them survived for as long as 5 years (Fig. 1). Aneurysmectomy (with coronary bypass in three patients) was performed in seven patients: in six for chronic congestive heart failure and in one for refractory arrhythmias; none of the seven was alive 1 year after operation.

Acute myocardial infarction recurred in two patients and was fatal in one. Thirteen patients died of refractory congestive heart failure; two died suddenly; six from noncardiac causes and one from rupture of the left ventricular aneurysm. In the latter patient a septic process involved the aneurysmal wall. Five of the seven patients undergoing aneurysmectomy died as a direct consequence of the operation, and the other two, from persistent chronic congestive heart failure.

The aneurysm was diagnosed clinically in 12 patients (43 percent): in 6 patients (21 percent), the electrocardiogram was consistent with aneurysm and in 3 (11 percent) the chest radiograph suggested aneurysm; the aneurysm was diagnosed with angiography in each of the 10 patients in whom this procedure was performed.

Examination of coronary arteries: The four major coronary arteries were examined in all 28 patients. In addition, in 22 patients in whom the entire lengths of the right, left main, left anterior descending and left circumflex coronary arteries were available, each of these four arteries was cut transversely into 5 mm long segments and each segment was labeled, processed for histologic study, and a histologic section stained by the Movat method[6] was prepared and examined.

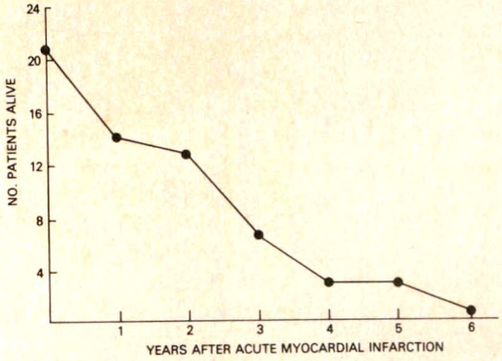


FIGURE 1. Length of survival after acute myocardial infarction in 21 necropsy patients with left ventricular aneurysm and unequivocal history of acute myocardial infarction.

TABLE II

Clinical and Cardiac Necropsy Observations in the 28 Patients

Case	Age (yr) & Sex	Clinically Diagnosed AMI	Interval (mo) AMI to Death	AP After AMI	Chronic CHF After AMI	Clinical Episode Compatible With SE	LV Angio-gram	Clinical Diagnosis of Aneurysm	History SH Before AMI	SAP >149/90 mm Hg After AMI	DM
Patients Without Left Ventricular Aneurysmectomy											
1	31M	+	36	0	+	0	+	+	−	0	0
2	39M	+	36	0	+	0	+	+	−	0	0
3	45M	+	3	0	+	0	0	0	+	0	0
4	46M	0	—[a]	0	0	0	0	0	+	0	0
5	46M	+	36	0	+	0	0	0	−	0	0
6	47M	+	6	0	+	0	0	0	+	+	0
7	57M	+	24	+	0	0	0	0	+	0	+
8	60F	+	7	0	+	0	+	+	+	0	0
9	61M	+	3	0	+	0	0	0	−		0
10	62M	0	—[a]	0	0	0	0	0	−	0	0
11	65M	+	3	0	+	+	0	0	+	0	0
12	68M	0	—[a]	0	+	0	0	0	−	0	+
13	69M	+	24	+	+	0	0	0	+	0	+
14	70M	+	23	0	+	0	0	+	+	+	0
15	71M	+	36	0	+	0	0	0	+	0	0
16	75M	0	—[a]	0	+	0	0	0	+	+	0
17	77M	+	6	0	+	0	0	0	−	0	0
18	78M	+	60	0	+	0	0	+	+	0	0
19	80M	0	—[a]	+	+	0	0	0	−	0	0
20	84M	0	—[a]	0	0	0	0	0	−	0	0
21	85F	0	—[a]	0	0	0	0	0	−	0	0
Patients With Left Ventricular Aneurysmectomy											
22	49M	+	60	0	+	0	+	+	−	0	0
23	55F	+	24	0	+	0	+	+	+	+	0
24	55M	+	24	+	+	0	+	+	−	0	+
25	56M	+	120	0	+	0	+	+	−	0	+
26	64M	+	8	0	0	0	+	+	−	0	0
27	67F	+	24	0	+	0	+	+	−	0	0
28	77M	+	26	0	+	0	+	+	+	0	0
Totals (or range)	31–85 24M, 4F	21	3–120	4	22	1	10	12	13	4	5
Percent	86M, 14F	75		14	79	4	36	43	46	14	18
Mean	62		28								

[a] Clinically silent acute myocardial infarction; [b] heart weight does not include operatively excised specimen.
AMI = acute myocardial infarct; AP = angina pectoris; CA = coronary arteries; CHF = congestive heart failure; DM = diabetes mellitus; LV

The degree of narrowing in all 5 mm long segments was determined by examination of the histologic sections magnified 25 to 50 times. *The percent of cross-sectional area narrowing* by atherosclerotic plaque was divided into four categories of narrowing: 0 to 25, 26 to 50, 51 to 75 and 76 to 100. The accuracy of these determinations was verified by random evaluations by other observers and by videoplanimetry, and both the intra- and interobserver error was less than 5 percent.[7]

Results

The ventricular aneurysm: The hearts in the 28 patients (Table II) weighed from 330 to 705 g (mean 523) and in 23 patients the weight was over 400 g. In 20 patients the aneurysm involved the *anterior* (11 patients) (Fig. 2), *posterior* (6 patients) (Fig. 2) or *lateral* (3 patients) (Fig. 3 and 4) walls of the *mid or basal third,* or both, of the left ventricle, with or without involvement of the apical third. In the other eight patients, the aneurysm was designated as *apical* because it involved mainly or only the apical third of the left ventricle, involving in each the entire wall in this portion of the heart (Fig. 5 and 6).

The coronary arteries: Among the 28 study patients (Table II), a total of 112 major (right, left main, left anterior descending and left circumflex) epicardial coronary arteries were examined. At least one of the four major epicardial coronary arteries was narrowed greater than 75 percent in cross-sectional area by atherosclerotic plaques in all 28 patients (Table III). Of the 112 major coronary arteries in the 28 patients, 71 (63 percent) were greater than 75 percent narrowed in cross-sectional area by atherosclerotic plaques, an average of 2.5 of 4.0 coronary arteries/patient. The left main coronary artery was narrowed greater than 75 percent in cross-sectional area in two patients.

Analysis of the 992 five mm long coronary arterial segments in 22 patients disclosed atherosclerotic narrowing of cross-sectional area of 76 to 100 percent in 323 segments (33 percent) 7 of 51 to 75 percent in 419 (42 percent), of 26 to 50 percent in 210 (21 percent) and of 0 to 25 percent in 40 (4 percent) (Table IV). The left anterior descending coronary artery was significantly ($p < 0.05$) more severely narrowed than the other three

TABLE II (continued)

Case	Mode of Death: SCD	AMI	Chronic CHF	Cardiac Op	Non-Cardiac Cause	LV Aneurysm Rupture	Heart Weight (g)	Site of LV Aneurysm	Thrombus in LV Aneurysm	LV Dilated	Number of 4 Major CA Narrowed 76–100% in XSA	Number of 5 mm Segments of CA Studied	Number (%) of 5 mm Segments Narrowed 76–100% in XSA
Patients Without Left Ventricular Aneurysmectomy													
1	0	0	+	0	0	0	520	Apical	0	+	2	56	8(14)
2	0	0	+	0	0	0	520	Apical	+	+	3	40	12(30)
3	0	0	+	0	0	0	500	Anterior	0	+	2	43	24(56)
4	+	0	0	0	0	0	380	Posterior	0	+	3	56	27(48)
5	0	0	+	0	0	0	500	Anterior	0	+	3	51	5(10)
6	0	0	+	0	0	0	465	Anterior	0	+	3	35	13(37)
7	0	+	0	0	0	0	575	Posterior	0	+	3	58	35(60)
8	0	0	+	0	0	0	530	Anterior	0	+	3	49	25(51)
9	0	0	+	0	0	0	530	Apical	+	+	2	–	–
10	0	0	0	0	+	0	500	Posterior	0	+	2	45	7(16)
11	0	0	+	0	0	0	430	Lateral	+	+	3	–	–
12	0	0	0	0	+	0	600	Posterior	0	+	3	–	–
13	0	0	+	0	0	0	430	Anterior	0	+	3	59	33(56)
14	0	0	+	0	0	0	618	Anterior	+	+	3	41	18(44)
15	0	0	0	0	+	0	360	Anterior	0	+	3	31	8(26)
16	+	0	0	0	0	0	670	Apical	+	0	3	63	27(43)
17	0	0	0	0	0	+	585	Lateral	+	+	3	43	7(16)
18	0	0	+	0	0	0	705	Apical	+	+	1	50	5(10)
19	0	0	0	0	+	0	330	Lateral	+	+	1	30	1(3)
20	0	0	0	0	+	0	390	Apical	0	0	3	–	–
21	0	0	0	0	+	0	380	Apical	+	+	2	13	8(61)
Patients With Left Ventricular Aneurysmectomy													
22	0	0	+	0	0	0	650[b]	Anterior	0	+	1	53	12(23)
23	0	0	0	+	0	0	500[b]	Posterior	0	+	3	–	–
24	0	0	0	+	0	0	700[b]	Anterior	+	+	3	54	6(11)
25	0	0	0	+	0	0	550[b]	Anterior	0	+	2	–	–
26	0	0	0	+	0	0	572	Anterior	0	+	2	29	15(51)
27	0	0	+	0	0	0	500[b]	Apical	0	+	2	48	6(13)
28	0	0	0	+	0	0	658	Posterior	+	+	4	45	21(47)
Totals (or range)	2	1	13	5	6	1	330–700		11	26	71	992	323
Percent	7	4	46	18	21	4			39	93			
Mean							523				2.5	45	15(33)

= left ventricular; mo = months; Op = operation; SAP = systolic arterial pressure; SCD = sudden coronary death; SE = systemic embolus; SH = systemic hypertension; Th = thrombus; XSA = cross-sectional area; + = present or positive; 0 = absent or negative; – = no information available.

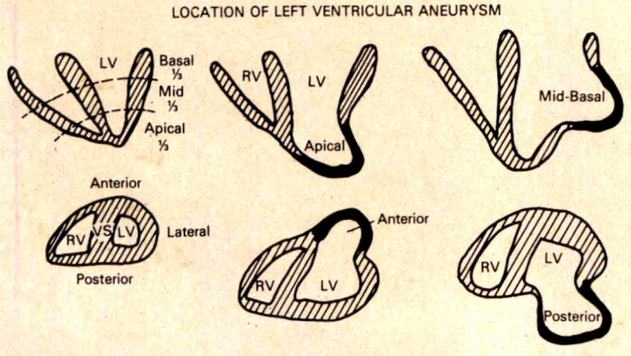


FIGURE 2. Locations of left ventricular aneurysms. The locations of apical (**top middle**) and mid-basal (**top right**) aneurysms are shown. The anterior, lateral and posterior walls of a transverse cardiac ventricular slice (**bottom left**) and the locations of anterior (**bottom middle**) and posterior (**bottom right**) wall aneurysms are shown. An aneurysm is considered anterior, posterior or lateral if it involves the anterior, posterior or lateral walls of the mid or basal third, or both, of the left ventricle with or without involvement of the apical third. An aneurysm is considered apical if it is limited to the apical third of the left ventricle. LV = left ventricle; RV = right ventricle; VS = ventricular septum.

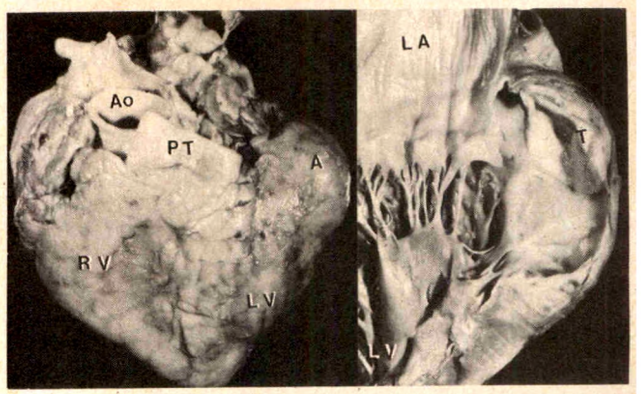


FIGURE 3. Patient 19 (Table II). Exterior view (**left**) and longitudinal section (**right**) of the heart from an 80 year old man (GT 72A-233) without a history of acute myocardial infarction but with angina pectoris and congestive heart failure. He died from carcinoma of the bladder. A lateral wall left ventricular aneurysm (A) that contains thrombus (T) is present. Ao = aorta; LA = left atrium; LV = left ventricle; PT = pulmonary trunk; RV = right ventricle.

major coronary arteries (Fig. 7). The mean percent of 5 mm segments severely narrowed in the proximal half of the right, left anterior descending and left circumflex coronary arteries was similar to that in the distal half of each of these arteries (Fig. 8).

Of the 22 patients in whom the amount of coronary arterial narrowing was quantified, 10 had an anterior, 6 an apical, 4 a posterior and 2 a lateral left ventricular aneurysm. In the 10 patients with an *anterior* left ventricular aneurysm, 79 (60 percent) of 132 five mm segments of the left anterior descending, 61 (34 percent) of 179 segments of the right and 19 (17 percent) of 115 segments of the left circumflex coronary artery were narrowed greater than 75 percent in cross-sectional area. In the 6 patients with an *apical* aneurysm, 35 (50 percent) of 70 segments of the left anterior descending, 17 (13 percent) of 130 segments of the right and 12 (20 percent) of 61 segments of the left circumflex coronary artery were narrowed greater than 75 percent. In the four patients with a *posterior* aneurysm, 26 (37 percent) of 71 segments of the left anterior descending, 40 (5(percent) of 80 segments of the right and 24 (50 percent of 48 segments of the left circumflex coronary artery were narrowed greater than 75 percent. In the two patients with a *lateral* aneurysm, 1 (4 percent) of 26 segments of the left anterior descending, 1 (3 percent) o 34 segments of the right and 6 (55 percent) of 11 segments of the left circumflex coronary artery were narrowed greater than 75 percent.

Comments

Clinical versus anatomic definition of ventricular aneurysm: Our study included only patients with a localized convex protrusion of the entire thickness of the left ventricular wall at necropsy. The wall of the aneurysm formerly was the wall of left ventricle, and the mouth of the aneurysm was larger than or as large as the maximal diameter of the aneurysm. These patients therefore had a *true anatomic* left ventricular aneurysm. When a localized left ventricular protrusion is

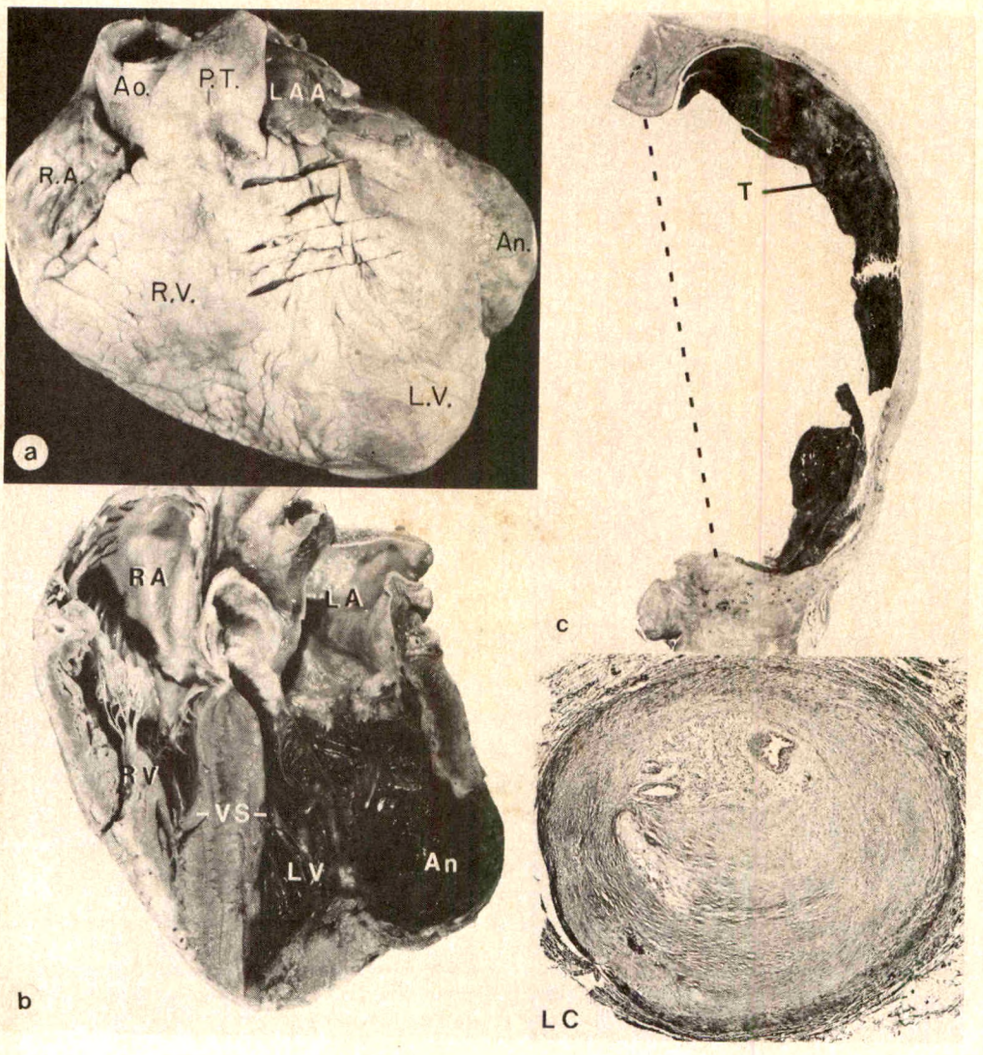


FIGURE 4. Patient 11 (Table II). Exterior view (**a**) and longitudinal section (**b**) of the heart and photomicrograph of the aneurysmal wall (**c**) and of the left circumflex (LC) coronary artery at point of maximal narrowing from a 65 year old man (A67–71) with no history of acute myocardial infarction or angina pectoris who died of progressive congestive heart failure. **a**, exterior view of the anterior surface of the heart showing the lateral wall left ventricular (L.V.) aneurysm (An.). **b**, longitudinal section of the heart showing the lateral wall left ventricular aneurysm and the dilated nonaneurysmal portion of the left ventricular cavity. VS = ventricular septum. **c**, histologic section of the scarred aneurysmal wall, the thrombus (T) adherent to its wall, and the mouth of the aneurysm (**dashed line**) (Movat stain ×2, reduced by 25 percent). ×2 **LC,** left circumflex coronary artery at its point of maximal narrowing. (Hematoxylin-eosin ×26, reduced by 25 percent. Ao = aorta; LA = left atrium; L.A.A. = left atrial appendage; P.T. = pulmonary trunk; R.A. = right atrium; R.V. = right ventricle; VS = ventricular septum.

present at necropsy, the protrusion must have been present during life in both ventricular systole and diastole. Patients in whom a localized protrusion is observed only during ventricular systole (*functional* aneurysm) would not have a protrusion at necropsy, and therefore such patients are not included in this analysis. Because the wall of the left ventricular aneurysm in our patients contained few if any myocardial fibers, the anatomic aneurysm could have been either akinetic or dyskinetic during life but not hypokinetic. Thus, clinical studies that have defined left ventricular aneurysm by hypokinetic wall motion abnormality or by akinetic or dyskinetic portions of wall,[8–16] without specifying protrusion during both phases of the cardiac cycle,[17–19] have included many patients without an anatomic aneurysm.

A precise definition of left ventricular aneurysm is crucial, in our view, because the findings to a large extent are dependent on the definition of aneurysm. In contrast to previous necropsy studies of patients with left ventricular aneurysm,[1–5,20] in our study all our patients had an aneurysm at the site of *healed* myocardial infarction and patients with an aneurysm at the sites of acute infarction were excluded. Additionally, our study excluded patients with associated noncoronary types of heart disease. Furthermore, in contrast to previous studies,[2,3,5] our study is based on personal examination of all the hearts of the patients included, rather than on examination of autopsy protocols, a recognized relatively inaccurate method of obtaining cardiovascular information.[21]

Pathologic Features

Characteristics of the aneurysm: In 27 of our 28 patients, the *left ventricular scars* involved more than 30 percent of the left ventricular wall. In none of five previously reported necropsy studies in English involving more than 20 patients[1–5] (Table I) was the size of the myocardial infarcts (which healed) quantified. However, in the study by Schlichter et al.,[2] the infarcts

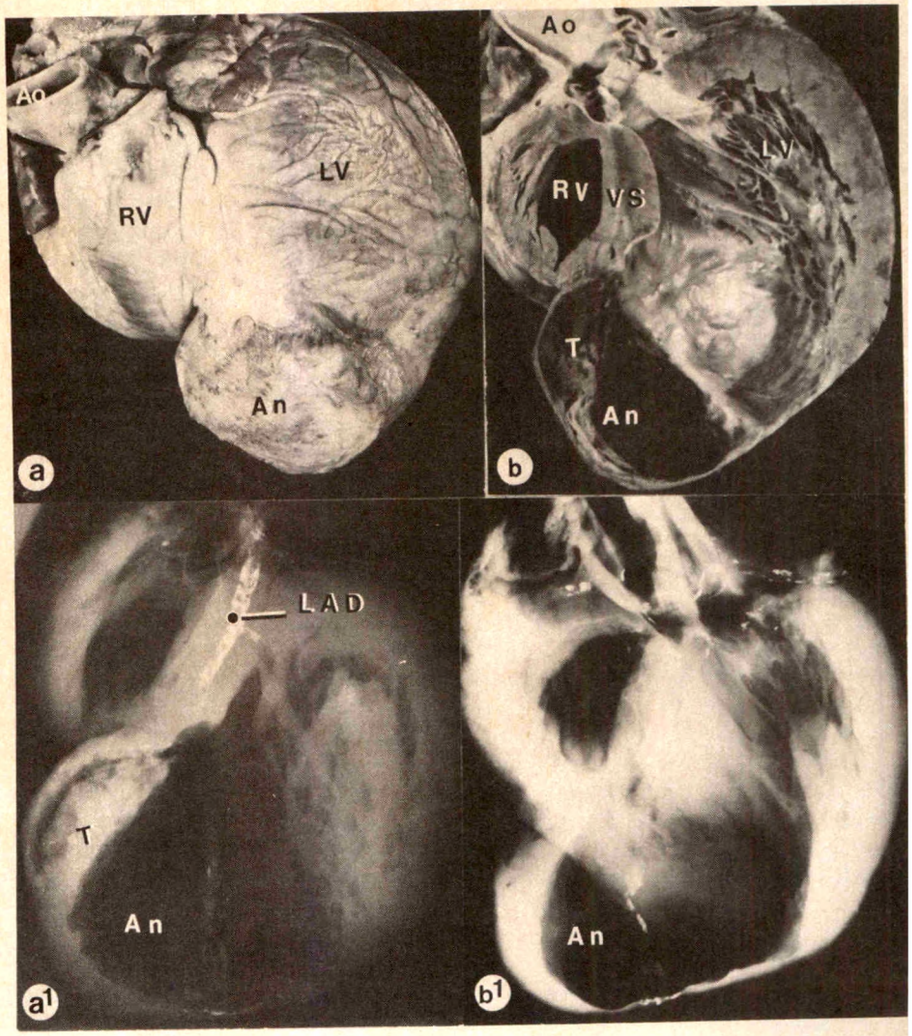


FIGURE 5. Patient 18 (Table II). Unopened heart and roentgenogram (**a** and **a**[1]) and after a longitudinal cut (**b**, **b**[1]) from a 78 year old man (GT 76A-171) who died of congestive heart failure 5 years after an acute myocardial infarction. **a**, exterior view of the heart showing a large apical wall left ventricular (LV) aneurysm (An). **a**[1], roentgenogram of **a** showing calcific deposits in the left anterior descending (LAD) coronary artery and in the wall of the aneurysm. The intraaneurysmal thrombus (T) also is seen. **b**, longitudinal section of the heart showing the apical aneurysm and the markedly dilated nonaneurysmal portion of the left ventricular cavity. **b**[1], roentgenogram of **b** showing calcific deposits in the coronary arteries and in the wall of the aneurysm. Ao = aorta; RV = right ventricle; VS = ventricular septum.

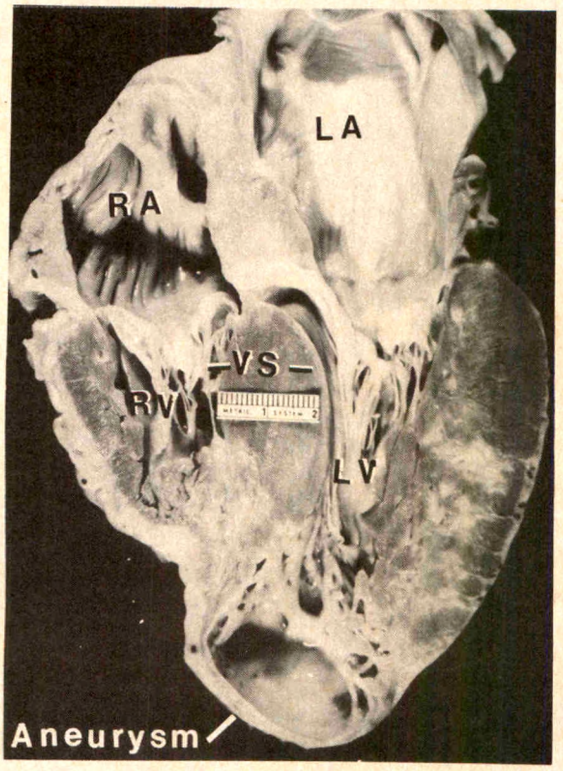


FIGURE 6. Patient 20 (Table II). Longitudinal section of the heart from an 80 year old man (GT 72A-219) who had no clinical evidence of coronary heart disease and died of acute pneumonia. An apical left ventricular (LV) aneurysm is present. The nonaneurysmal wall is hypertrophied and the left ventricular cavity is not dilated. LA = left atrium; RA = right atrium; RV = right ventricle; VS = ventricular septum.

were described as "large," apparently in most patients.

Scarring in portions of the left ventricular wall not involved in or adjacent to the aneurysm was absent in our 28 patients. This finding was not reported in previous studies[1–5,20,22–24] of necropsy patients with left ventricular aneurysm. The significance of this observation is that the aneurysm represents, with few exceptions, the only myocardial infarction that occurred.

The nonaneurysmal portion of the left ventricular wall was hypertrophied in 24 (86 percent) of our 28 patients and the *heart weight was increased* (greater than 350 g in women and greater than 400 g in men). In 20 of the 24 patients, the heart weighed 500 g or more. Only two of five previous necropsy studies (Table I) mentioned heart weight. Phares et al.[1] found the heart weight to be "100 grams or more above the predicted normal" in 33 (83 percent) of 40 patients and Dubnow et al.,[4] found it "100 grams or more above expected normal" in 66 (83 percent) of their 80 patients.

The portion of left ventricular cavity uninvolved by aneurysm was dilated in 26 (93 percent) of our 28 patients. Information on left ventricular cavity size is lacking in previous necropsy studies of patients with left ventricular aneurysm[1–5,20,22–24] (Table I).

TABLE III

Number of 28 Patients With Severe* Narrowing of One or More Major Coronary Arteries and Number of 112 Major Coronary Arteries With Such Narrowing

Number of Coronary Arteries With Severe Narrowing	Number of Patients	Total Number of Coronary of Arteries (4/patient)	Total Number of Coronary Arteries With Severe Narrowing
1	3	12	3
2	8	32	16
3	16	64	48 } 2.5/4.0
4	1	4	4
Totals	28	112	71 (63%)

* 75 percent or greater narrowing of cross-sectional area.

Characteristics of the coronary arteries: *Th degree of narrowing of the epicardial coronary arterie* in necropsy patients with healed left ventricular aneurysm was recognized as "severe" in previous studie (Table I)[1,2,4,5] as well as in our patients. Phares et al. mentioned "severe" narrowing of the left anterior descending coronary artery in a "majority" of their 4(patients. Schlichter et al.[2] described "severe" coronary narrowing in an unspecified number of their 102 patients. Dubnow et al.[4] described "occlusive lesions" in one or more coronary arteries in all of their 80 patients and Davis and Ebert[5] reported greater than 50 percent luminal narrowing (whether cross-sectional area or diameter reduction not specified) in two or more of the three major (left anterior descending, left circumflex and right) coronary arteries in 20 of their 24 necropsy patients. In 25 of our 28 patients, two or three of the three major coronary arteries were narrowed greater than 75 percent in cross-sectional area by atherosclerotic plaques, and in the other 3 patients, only one artery was similarly narrowed.

Although several previous studies have superficially mentioned degrees of coronary narrowing in necropsy patients with left ventricular aneurysm, *quantitative information on the extent and distribution of the narrowing in each of the four major coronary arteries* has not been reported previously. In 22 of our 28 patients, an average of 33 percent (range 3 to 61) of the lengths of the four major arteries were narrowed 76 to 100 percent and another 42 percent were narrowed 51 to 75 percent in cross-sectional area by atherosclerotic plaque. The left anterior descending artery had significantly more 5 mm long segments narrowed severely (greater than 75 percent) than did the other major arteries. This was true for the patients with an anterior wall or apical aneurysm (16 patients) but not in the patients with a posterior or lateral wall aneurysm (6 patients).

Clinical Features

Sex and age: It is well recognized that coronary heart disease is more frequent in men than in women by a ratio of about 2:1. Among necropsy patients with left

TABLE IV

Number and Percent of 5 mm Long Segments of the Four Major Epicardial Coronary Arteries With the Four Grades of Cross-Sectional Area Luminal Narrowing*

Coronary Artery	Percent Cross-Sectional Area Luminal Narrowing				
	0–25	26–50	51–75	76–100	Totals
Left main					
n	1	14	18	2	35
%	(3)	(40)	(51)	(6)	(100)
Left anterior descending					
n	11	45	102	141	299
%	(4)	(15)	(34)	(47)	(100)
Left circumflex					
n	17	54	103	61	235
%	(7)	(23)	(44)	(26)	(100)
Right					
n	11	97	196	119	423
%	(3)	(23)	(46)	(28)	(100)
Totals					
n	40	210	419	323	992
%	(4)	(21)	(42)	(33)	(100)

* Data based on 22 patients.

ventricular aneurysm, this sex difference is more pronounced. Of our 28 patients, 24 were men and 4 were women (Table II), yielding a man to woman ratio of 6:1. Of the 287 necropsy patients with left ventricular aneurysm reported on in four previous studies[1–4] (Table I), 224 (78 percent) were men and 63 (22 percent) were women. Of necropsy patients with fatal coronary heart disease, those with compared to those without left ventricular aneurysm tend to be older. The mean age of 185 necropsy patients with left ventricular aneurysm from three previously reported studies[1,3,4] was 69 years. The mean age of our 28 patients was 62 years (range 31 to 85), and 17 (61 percent) were 60 years of age or older (Table II).

Heart failure and angina: *Chronic congestive heart failure* was the most frequent manifestation of cardiac dysfunction in our patients, occurring in 22 (79 percent) of the 28. In contrast, angina pectoris was present in only 4 (14 percent) of the 28 patients and in each of them it was infrequent (Table II). Other investigators have also noted a high frequency of chronic congestive heart failure in their patients: in 24 (60 percent) of 40 patients[1]; in 71 (71 percent) of 102 patients[2]; in at least 61 (75 percent) of 80 patients[4]; and in 35 (88 percent) of 40 patients[5] (Table I). The frequency of angina pectoris in necropsy patients with left ventricular aneurysm has rarely been mentioned. Davis and Ebert[5] recorded angina in 25 (63 percent) of their 40 patients reported

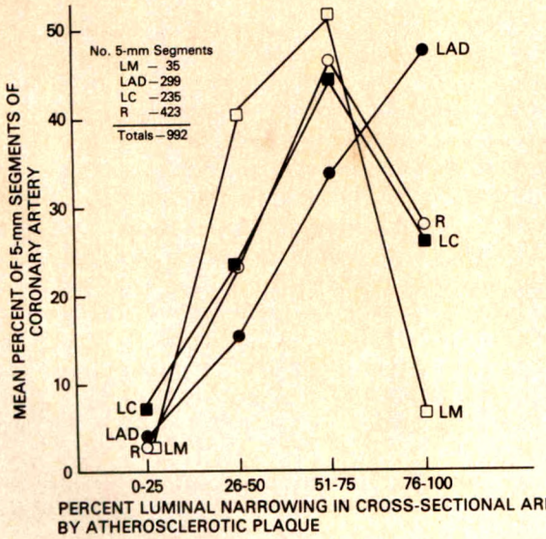


FIGURE 7. Mean percent of 5 mm long segments of the left main (LM), left anterior descending (LAD), left circumflex (LC), and right (R) coronary arteries narrowed to various degrees in 22 study patients with healed myocardial infarction and left ventricular aneurysm.

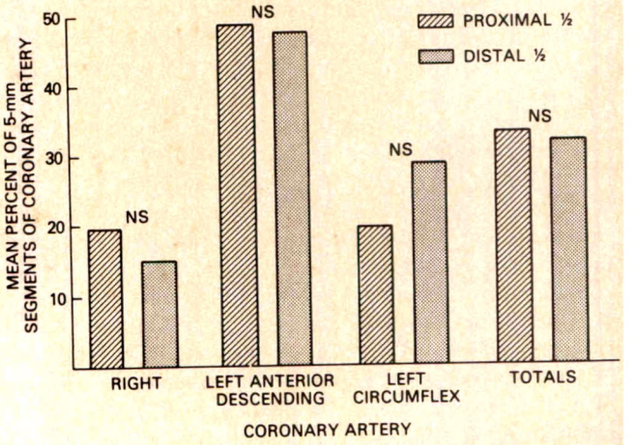


FIGURE 8. Mean percent of 5 mm long segments of the right, left anterior descending and left circumflex coronary arteries narrowed more than 75 percent in cross-sectional area by atherosclerotic plaques in the proximal and distal halves of each artery in 22 study patients with healed myocardial infarction and left ventricular aneurysm. NS = no significant difference.

to have left ventricular aneurysm, but the criteria for diagnosis of aneurysm in their patients were imprecise. Phares et al.[1] found severe angina in 5 (13 percent) of their 40 patients. All our patients with chronic congestive heart failure had dilated nonaneurysmal portions of left ventricle, in general a fairly reliable anatomic indicator for the presence of chronic congestive heart failure in patients without valvular heart disease or intercirculatory shunts. It appears that the dilated left ventricle even in patients with severely narrowed coronary arteries infrequently causes angina pectoris, and when it does, the angina is mild and infrequent.

Systemic hypertension: This was present in at least 13 of our 28 patients before the acute myocardial infarction and in the remaining 15 patients information regarding the level of the systemic blood pressure before the infarction was inadequate. Only four patients had systemic hypertension after healing of the acute infarction (Table II). Thus, systemic hypertension is infrequent in patients with healed myocardial infarction and true left ventricular aneurysm. It seems likely that the explanation for the considerable cardiomegaly in most of our patients was the presence of systemic hypertension, undiagnosed in most, before the acute myocardial infarction. Also, it is likely that the poorly contracting aneurysmally dilated left ventricle after healing of the acute infarction was incapable of creating sufficient cardiac output to allow elevation of the systemic arterial pressures. The frequency of systemic hypertension in previously described necropsy patients with left ventricular aneurysm has ranged from 22 percent (14 of 65 patients)[3] to 68 percent (69 of 102 patients).[2] It is not apparent from these previous studies[1–4] (Table I) whether the systemic hypertension was present before or after the acute myocardial infarction, or both, or whether the information was derived by history or by actual blood pressure recording.

Thromboembolism: Although left ventricular aneurysms frequently contain thrombi, the frequency of *clinical events compatible with systemic emboli* is quite variable. Of our 28 patients, 11 (39 percent) had intraaneurysmal thrombi but only 1 had an event compatible with a systemic embolus; none of the 17 patients without intraaneurysmal thrombi had a compatible event (Table II). Of 102 patients with left ventricular aneurysm reported by Schlichter et al.,[2] 55 (54 percent had intraaneurysmal thrombi; and at least 36 (35 percent) of their 102 patients had a clinical event compatible with a systemic embolus. Of the 80 patients reported on by Dubnow et al.,[4] 52 (65%) had intraaneurysmal thrombi, and 10 (minimum) had a clinical embolic event. Only 9 (14 percent) of the 65 patients described by Abrams et al.[3] had intraaneurysmal thrombi, and the frequency of clinical systemic emboli was not mentioned (Table I). Despite the variability in the reported frequency of clinical events compatible with systemic emboli in patients with left ventricular aneurysm and healed myocardial infarction, intraaneurysmal thrombus formation is frequent and it would, therefore, appear reasonable to use anticoagulant agents in thes patients.

Clinical diagnosis: Surprisingly, clinical diagnosi of left ventricular aneurysm by means other than lef ventricular angiography is infrequent. The diagnosis o left ventricular aneurysm was made in each of our 1(patients who underwent left ventricular angiograph; but among the other 18 patients, diagnosis by ches radiograph or electrocardiogram was made in only 2 Persistent S-T elevation in the electrocardiogram afte healing of the acute myocardial infarction was observe in only 6 (21 percent) (4 of whom also had angiography of our 28 patients. In previous studies clinical diagnosi of left ventricular aneurysm was made in only 4 (6 per cent) of 65 necropsy patients,[3] in 13 (16 percent) of 8(necropsy patients,[4] and in 6 (22 percent) of 27 necropsy patients[5] (Table I).

Prognosis: *Survival* in patients who manifest a lef ventricular aneurysm after a clinically documente acute myocardial infarction is clearly diminishe compared with that in patients with healed myocardia infarction unassociated with aneurysm. Of our 21 pa tients whose acute infarction was diagnosed clinically only 3 lived 60 months or longer thereafter (Fig. 1). Ir previous studies of patients with left ventricular aneu rysm and earlier clinical documentation of acute myo cardial infarction, only 8 (12 percent) of 66[2] and 13 (27 percent) of 48[4] survived 5 years or longer after infarctior (Table I).

Causes of death: It is well recognized that most pa tients with severe coronary arterial narrowing from atherosclerosis either die suddenly, from so-called sudden coronary death or from acute myocardial infarction. This situation holds whether the coronary event is a first or a subsequent one. Such, however, was not the situation among our patients with left ventricular aneurysm and healed myocardial infarction (Table II). Only 2 of our 28 patients died suddenly, and only 1 had a fatal acute myocardial infarction. Thirteen of our 28 patients died from intractable congestive heart failure and 5 from consequences of left ventricular aneurysmectomy. It is likely that congestive heart failure would have proved fatal in at least four of these latter five patients. Rupture of a healed true left ventricular aneurysm is an extremely rare occurrence. Rupture did occur, however, in one of our patients but only because septicemia developed and a septic process invaded the aneurysmal wall. Chronic congestive heart failure was not as frequent a fatal event, and fatal acute myocardial infarction was more frequent in previous necropsy studies[1,3–5] (Table I). "Sudden coronary death" was noted to be an infrequent mode of death in previous reports (6 [15 percent] of 40 patients,[1] none of 102 patients,[2] none of 65 patients[3] and none of 24 patients).[5]

Conclusions: Thus, from our study of 28 necropsy patients with true anatomic left ventricular aneurysm and healed myocardial infarction, the following conclusions appear justified: The myocardial infarct is large; the heart weight is increased and the nonscarred

left ventricular wall is hypertrophied; the nonaneurysmal portions of the left ventricular cavities are dilated; the major epicardial coronary arteries are severely narrowed; chronic congestive heart failure is frequent and is the most common cause of death; angina pectoris is infrequent; recurrence of acute myocardial infarction is infrequent; clinical events compatible with systemic emboli are infrequent despite frequent intraaneurysmal thrombus; the long-term prognosis is poor; sudden death is infrequent; and clinical diagnosis of the left ventricular aneurysm without left ventricular angiography is infrequent.

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Response to Exercise Early After Uncomplicated Acute Myocardial Infarction in Patients Receiving No Medication: Long-Term Follow-Up

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Cardiovascular function and prognosis have not been adequately defined early after an uncomplicated acute myocardial infarction in patients given no medication. Ninety such patients were studied with treadmill testing submaximally at 3 weeks and maximally at 8 weeks after infarction. The exercise heart rate, rate-pressure product and oxygen uptake were, respectively, 120 ± 17 beats/min, 179 ± 43 and 17.4 ± 1.0 ml/kg per min at 3 weeks and 157 ± 20, 271 ± 55 and 24.3 ± 3.7 at 8 weeks. Exercise variables at submaximal equivalent exercise work did not change from 3 to 8 weeks. At maximal exercise 15.6 percent of patients had S-T changes alone, 8.9 percent had angina alone and 12.2 percent had both. Patients were followed up for a mean of 23.7 months for complications—death, reinfarction, bypass grafting and progression to functional class III and IV. Complications occurred in 27 percent of patients with both angina and S-T changes, 29 percent of those with S-T changes alone, 25 percent of those with angina alone, 8 percent of those with ventricular arrhythmia alone, 12 percent of those with a normal 8 week treadmill test and in 17 percent of the group as a whole. Another 18 patients who were given no medication and whose course was uncomplicated could not perform a maximal 8 week treadmill test because of angina pectoris or S-T segment depression, or both, and 56 percent of these had long-term complications.

In conclusion, these reference values serve as safe limits in performing treadmill testing early after acute myocardial infarction. S-T changes or angina, or both, and inability to complete a maximal 8 week treadmill test identify patients at risk for later complications even though these patients may have been considered to be in a low risk category clinically.

Cardiovascular function has not been completely defined in the early period after an acute myocardial infarction. Until recently, exercise testing has been used primarily to study patients suspected of having clinical or subclinical coronary artery disease. Exercise tests in the early period after acute myocardial infarction are now being performed and the data obtained frequently reported.[1–13] Reliable baseline responses to assess abnormal values have not been published and long-term follow-up results have not been described. A reliable reference group of patients studied after acute myocardial infarction is needed as a standard for comparison before exercise treadmill testing is used in this early period for diagnostic purposes. Safe limits must be determined.

In this paper we define exercise variables in patients who had an uncomplicated acute myocardial infarction and who underwent treadmill exercise testing submaximally at 3 weeks and maximally at 8 weeks after infarction. We propose to assess the exercise capacity of these patients after an acute myocardial infarction as has been done for normal subjects and patients with chronic coronary artery disease[14,15] and to correlate these data with long-term follow-up.

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Methods

Study patients: One hundred eight patients, 93 men and 15 women, were studied. Their average age was 53 ± 10 years (range 30 to 79). All patients had an uncomplicated acute myocardial infarction; that is, none had congestive heart failure or angina pectoris during rehabilitation.

The diagnosis of an acute transmural myocardial infarction was substantiated by all of the following: chest pain typical of coronary artery disease, serial acute serum enzyme changes and evolving Q wave abnormality with acute S-T and T wave changes in the electrocardiogram. The diagnosis of subendocardial myocardial infarction was substantiated with chest pain typical of coronary artery disease, serial diagnostic enzyme changes, and acute S-T and T wave changes persisting for more than 48 hours. No patient had a history of angina pectoris during rehabilitation after myocardial infarction. Three patients had mild cardiomegaly on chest X-ray examination, as defined by a cardiothoracic ratio greater than 50 percent, but none had clinical evidence of congestive heart failure. No patient was taking digitalis, propranolol or any antiarrhythmic agent. No history of syncope or other cardiac disease was elicited. No patient had undergone previous coronary bypass surgery. Mitral valve prolapse and valvular heart disease were absent.

Classified functionally according to New York Heart Association[16] *criteria at the 8th week after acute myocardial infarction,* 59 were in class I, 49 in class II, and none in class III or IV. No patient had been under treatment for ventricular arrhythmia, angina pectoris or congestive heart failure. The site of the recent myocardial infarction was anterior in 30, inferior or posterior, or both, in 52 and subendocardial in 26 patients.

The study group was derived from 410 patients who entered Wilford Hall U. S. Air Force Medical Center between October 1975 and March 1978 with a transmural or subendocardial acute myocardial infarction. Other patients with uncomplicated myocardial infarction were not studied because they were taking cardiotropic medications. The patients were studied with exercise stress testing at 3 and 8 weeks after infarction. Progressive rehabilitation with passive and active range of motion exercises was started in the coronary care unit. After discharge from the unit, the patients were gradually allowed to walk and, by the 3rd week, they were walking 1 mile daily without cardiovascular symptoms.

Treadmill testing: The procedure was performed in the fasting subjects in the morning, and it was usually their first experience with treadmill walking. They were not allowed to support their weight on the handrails. Subjects with any of the following findings were excluded from our "standard" study: (1) any physical ailment that could limit treadmill performance; (2) a submaximal treadmill effort, as judged by those monitoring the treadmill test; (3) an electrocardiogram at rest showing a bundle branch block pattern; and (4) blood pressure at rest greater than 140/90 mm Hg. The study purpose and details were explained, and informed consent was obtained from each patient according to the Wilford Hall Medical Center Human Experimentation Committee.

Exercise protocol: An electrocardiogram during exercise was continuously monitored using a Mason-Likar 12 lead system.[17] The exercise test at the 3rd week after myocardial infarction consisted of three minute stages at 1.7 miles/hour with grades of 0, 5 and 10 percent, respectively. At the 8th week after infarction, the patients underwent a maximal Bruce treadmill test[18] after going through the initial stages of the 3rd week protocol. No complications were encountered. The exercise tests at 8 weeks were maximal; that is, they were symptom-limited or limited by the development of progressive angina pectoris, S-T segment depression greater than 4 mm S-T or a decrease in systolic blood pressure of more than 10 mm Hg. Electrocardiographic recordings were made before exercise in the lying and standing positions, during the last 30 seconds of each level of exercise, during the immediate postexercise period, and every 3 minutes thereafter until ventricular ectopic status or S-T segment changes had returned to control level. Blood pressure cuff recordings were obtained at 1 to 3 minutes intervals throughout the exercise period.

Ninety of the 108 patients with uncomplicated myocardial infarctions were able to exercise for the total 9 minutes of our 3 week treadmill testing protocol and maximally at 8 weeks. These 90 patients are the source of our baseline standard of exercise responses for patients after myocardial infarction. The 18 patients unable to exercise maximally at 8 weeks were limited by angina alone (8 patients), both angina and S-T segment depression (8 patients) or S-T depression alone (2 patients). The condition of all these patients had been considered clinically uncomplicated.

For statistical analysis, we used the unpaired *t* test. Subgroup sample sizes were too small for chi-square analysis.

Results

Exercise Test Results

S-T depression and angina: None of the 90 study patients were limited by angina pectoris at the 3rd or 8th week of exercise. In all, fatigue, progressive shortness of breath or leg discomfort was the exercise end point. Angina pectoris developed in 9 patients (10 percent) at 3 weeks and in 19 patients (21 percent) at 8 weeks with maximal exercise. These patients who experienced angina at maximal exercise denied the presence of angina except during the exercise testing. One mm or greater S-T segment depression occurred in 3 patients (3 percent) at 3 weeks and in 25 patients (27 percent) at 8 weeks with maximal exercise. Two mm or greater S-T segment depression occurred in no patient at 3 weeks and in eight patients (9 percent) at 8 weeks. Thirteen patients had S-T elevation with exercise. All but three of these also had S-T depression. In two of these three, the S-T elevation was in leads corresponding to a prior anterior infarction.

Evidence of ischemia (presence of angina or S-T segment displacement 1 mm or greater from resting values) was seen in 13 percent of patients at 3 weeks and in 30 percent of patients at 8 weeks in the 90 reference patients. Ischemia was present in 18 (100 percent) of 18 patients not exercising maximally at 8 weeks.

Ventricular arrhythmia: Table I shows the results of ventricular arrhythmia analysis in the 90 patients. The variables assessed were the presence of any premature ventricular complexes, more than three premature ventricular complexes/min, multifocal premature ventricular complexes, bigeminy, couplets and ventricular tachycardia (three or more consecutive beats). In more than half (50) of the patients, premature ventricular complexes developed with exercise; however, these complexes were reproducible from the 3rd to the 8th week in only 16 (32 percent) of the 50. Bigeminy and couplets occurred in 13 and 11 percent of patients, respectively. The type and prevalence of premature ventricular complexes did not change significantly in

TABLE I

Premature Ventricular Complex Analysis at 3 and 8 Weeks After Acute Myocardial Infarction in 90 Patients

	3rd Week Only (%)*	8th Week Only (%)*	3rd & 8th Week (%)*	Total (%)†
Any premature ventricular complex	16 (32)	18 (36)	16 (32)	50 (54)
3/min or greater	7 (25)	13 (46)	8 (29)	28 (30)
Multifocal	1 (14)	5 (71)	1 (14)	7 (8)
Bigeminy	5 (42)	4 (33)	3 (25)	12 (13)
Couplets	3 (30)	4 (40)	3 (30)	10 (11)
Ventricular tachycardia	0	1 (100)	0	1 (1)

* Percent of the total number of patients having each type of arrhythmia. † Percent of total patients (90).

TABLE II

Hemodynamic Exercise Responses* After Acute Myocardial Infarction in 90 Patients

	3rd Week	8th Week
Heart rate (beats/min)		
At rest	72 ± 12	73 ± 11
Maximal	120 ± 17	157 ± 20
Systolic blood pressure (mm Hg)		
At rest	112 ± 16	116 ± 15
Maximal	148 ± 23	173 ± 22
Rate-pressure product		
Maximal	179 ± 43	271 ± 55
Percent increase from resting	225 ± 52	327 ± 74
Estimated oxygen consumption (ml/kg per min)	17.4 ± 1.0	24.0 ± 3.7
Exercise time (s)	540	746 ± 106

* Mean ± 1 standard deviation.

the group as a whole from the 3rd to the 8th week. Ventricular tachycardia was a rare occurrence. No sustained arrhythmia was encountered and there was no arrhythmic morbidity.

Hemodynamic responses: The hemodynamic responses to exercise as evaluated by heart rate, systolic blood pressure, rate-pressure product, estimated oxygen consumption[14] and exercise time are shown in Table II, where values are assessed as mean ± 1 standard deviation, and in Table III, where values are shown for the 10th, 50th (median) and 90th percentiles. All patients had these measurements at both the 3rd and 8th week after myocardial infarction. No patient experienced a decrease in heart rate or systolic blood pressure with exercise at any stage. There was no significant difference in the heart rate, systolic blood pressure or maximal rate-pressure product at 3 weeks between the 90 patients forming the baseline standards and the 18 patients who were unable to exercise maximally at 8 weeks. However, the 8 week values in the 18 patients were lower because ischemia limited their testing.

The heart rate and rate-pressure product at the same 9 minute exercise time (1.7 miles/h, 10 percent grade) at both the 3rd and the 8th week were compared to detect any serial change in these functions at an equivalent work load. There was no significant change in these values from the 3rd to the 8th week.

Relation to age and infarct location (Table IV): Duration of exercise at the 8th week (Bruce protocol) increased significantly with decreasing age. Maximal heart rate, oxygen consumption and rate-pressure product at the 8th week were also age-related, with decreasing values as age increased. The older the patient, the closer to a maximal value was his exercise response when the modified 3rd week treadmill protocol was used. There was not a wide individual variation within age groups of any of the variables studied. There was no relation between the estimated oxygen uptake, the maximal heart rate or rate-pressure product determination and site of infarction. Subgroups other than those related to age are not specifically identified because the population is homogeneous.

Clinical follow-up results: All 108 patients were followed up for a mean of 23.7 months. The complications assessed during the follow-up period were death, reinfarction, aortocoronary saphenous vein bypass grafting (for severe limiting angina only) or progression to clinical functional class III or IV. Death occurred in only two patients, one with S-T depression only and one with neither angina nor S-T depression on exercise. Among the 90 patients exercising maximally (not limited by cardiovascular symptoms or signs), complications occurred in 27 percent of those with both angina and S-T depression, in 29 percent of those with S-T segment depression only, in 25 percent of those with angina only, in 8 percent of those with ventricular arrhythmia only, in 12 percent of those with a normal exercise response and in 17 percent of the group as a

TABLE III

Maximal Hemodynamic Exercise Responses* After Acute Myocardial Infarction in 90 Patients

	10th Percentile		50th Percentile		90th Percentile	
	3 Weeks	8 Weeks	3 Weeks	8 Weeks	3 Weeks	8 Weeks
Heart rate (beats/min)	100	132	120	160	146	180
Systolic blood pressure (mm Hg)	120	150	150	170	180	200
Estimated oxygen consumption (ml/kg per min)	15.2	18.9	17.6	24.2	18.3	29.4
Exercise time (s)	540	600	540	750	540	900

* 10th, 50th and 90th percentiles.

TABLE IV

Age-Related Exercise Variables After Acute Myocardial Infarction in 90 Patients

Patients (n)	Age (yr)	Exercise Time (8 Week) (s)	Maximal Heart Rate (beats/min)		Estimated Oxygen Consumption (ml/kg per min)		Rate-Pressure Product (units)	
			3 Week	8 Week	3 Week	8 Week	3 Week	8 Week
5	39	514 ± 110	112 ± 13	185 ± 15	18.6 ± 0.3	28.5 ± 3.8	150 ± 12	320 ± 57
24	40–49	428 ± 102	121 ± 19	163 ± 21	17.8 ± 0.9	25.5 ± 3.6	171 ± 50	271 ± 60
37	50–59	407 ± 74	118 ± 17	159 ± 15	17.4 ± 0.8	24.8 ± 2.6	178 ± 43	289 ± 45
21	60–69	294 ± 80	126 ± 17	145 ± 20	16.7 ± 1.2	20.8 ± 2.8	191 ± 39	244 ± 39
4	70–79	270 ± 95	109 ± 13	130 ± 13	16.6 ± 1.0	20.0 ± 3.3	176 ± 24	217 ± 67
Total mean		388	120 ± 17	157 ± 20	17.4 ± 1.0	24.0 ± 3.7	179 ± 43	271 ± 55

whole. The occurrence of long-term complications in patients with an ischemic 8 week test response was significantly greater than that in patients with a nonischemic response ($p < 0.05$). Among the other 18 patients who had no medication and whose course was also considered uncomplicated but who were limited at the 8th week exercise test by cardiovascular signs or symptoms, 10 (56 percent) had long-term complications. This incidence was significantly greater than that in patients with a nonischemic 8 week test ($p < 0.001$). The site of myocardial infarction in these 18 patients was inferior in 61 percent, anterior in 28 percent and subendocardial in 11 percent. Four of the 13 patients with exercise-induced S-T elevation had long-term complications, but all 4 also had S-T depression.

Discussion

Features of our study group: The predominance in our series of patients with an inferior or posterior site of myocardial infarction probably reflects our exclusion of patients with clinical heart failure from the study. The preponderance of inferior myocardial infarction is similar to that in other postmyocardial infarction exercise studies.[9,11,19,20] Inferior infarction was also predominant in the 18 patients who had the highest complication rate.

Our patients were a select group with uncomplicated myocardial infarction. No patient was taking digitalis, propranolol or an antiarrhythmic agent. In all past studies there was no medication control; up to 23 percent of patients reported on were taking antiarrhythmic drugs or propranolol and up to 66 percent were taking digitalis.[7–13] These medications could exert profound effects on the presence of angina pectoris, ischemic electrocardiographic and heart rate responses, exercise duration, and presence of arrhythmias. Attrition has occurred in previous serial studies[9,10,19]; however, none occurred in out patient group.

Comparison of 3 week and 8 week exercise tests: Table V compares the age-related maximal heart rate of our patients tested 8 weeks after acute infarction with data obtained from previous exercise studies of normal subjects[21] and patients tested 3 weeks after infarction.[5] In all age decades the mean maximal heart rate in patients who have had a myocardial infarction was less than that in normal subjects.

Early after myocardial infarction, our patients had a maximal exercise performance essentially equivalent to that of patients studied more than 3 months after infarction[4,14,15] (Table VI). In our subjects, the mean maximal heart rate at 8 weeks after infarction was higher than that observed by Ibsen et al.[5] during maximal exercise treadmill testing at 3 weeks. Their results may have been influenced by the 19 percent of patients who were taking digitalis and 3 percent taking propranolol, and inclusion of patients with myocardial dysfunction.

At submaximal equivalent exercise work loads, there was no significant difference in the exercise variables studied from the 3rd to the 8th week in our reference population. This finding is at variance with that of other investigations. The study by Markiewicz et al.[9] with serial submaximal treadmill testing in 46 patients (23 of whom had symptom-limited tests) after acute myocardial infarction showed that the aerobic capacity improved from the 3rd to the 8th week. Wohl et al.[19] also

TABLE V

Maximal Exercise Heart Rates (beats/min) by Age

	Age Decade					
	20–29	30–39	40–49	50–59	60–69	70–79
Normal subjects[21]	190	182	179	171	164	—
8 weeks after acute myocardial infarction*	—	185 ± 15	163 ± 21	159 ± 15	145 ± 20	130 ± 13
3 weeks after acute myocardial infarction[5]	—	—	144 ± 18	133 ± 16	125 ± 17	115 ± 14

* Present series.

TABLE VI

Summary of Exercise Variables in Various Patient Populations

Study	Age (yr)	n	Resting Heart Rate (beats/min)	Maximal Heart Rate (beats/min)	Pressure-Rate Product (units)	Estimated Maximal Oxygen Consumption (ml/kg per min)	Exercise Duration* (s)
Sedentary normal subjects[15]	55 ± 8	69	—	170 ± 18	—	33.9 ± 6.3	547 ± 115
Chronic coronary artery disease[15]	50 ± 7	249	74 ± 12	156 ± 20	252 ± 56	25 ± 9	454 ± 156
12 weeks after acute myocardial infarction[4]	50	216	74 ± 12	149 ± 25	283 ± 70	21.3 ± 5.9	—
12 weeks after acute myocardial infarction (fatigue-limited)[4]	50	99	74 ± 12	164 ± 17	324 ± 51	24.9 ± 4.6	—
Healed acute myocardial infarction[14]	58 ± 8	21	—	161 ± 14	—	28.1 ± 6.8	418 ± 139
Present series	55 ± 10	90	73 ± 11	157 ± 20	271 ± 55	24.3 ± 4	386 ± 106

* Bruce treadmill protocol.

noted improvement early after infarction but showed a more favorable myocardial oxygen supply-demand ratio from the 3 to 6 week study to the 3 to 6 month study because of improvement in myocardial function. The exercise in approximately 50 percent of their patients was limited by symptoms and signs suggestive of myocardial ischemia at peak exercise. Many patients were taking cardiotropic agents, and patients in functional class III were included in their study. None of our patients were similarly limited, although 30 percent had signs of ischemia at peak exercise.

Ischemic changes during exercise early after infarction: Studies of exercise testing after myocardial infarction have shown that angina is produced in 9 to 21 percent of patients at 3 weeks.[3,5,6,9,10,12] Angina developed in 10 percent of our reference patients at 3 weeks and in 21 percent at 8 weeks after myocardial infarction. Abnormal S-T segment response with exercise occurs in 13 to 49 percent of patients at 3 weeks, occurring in most with maximal exercise.[3,5,6,9,10,12] One mm or more S-T segment depression was seen in only 3 percent of our reference patients at 3 weeks and in 28 percent at 8 weeks after acute myocardial infarction. No serious ischemic complications were seen in any post-infarction exercise study. Our study shows that ischemic exercise changes in patients with uncomplicated infarction are rarely present at 3 weeks after acute infarction, and that more ischemia is evident at the higher exercise work load at 8 weeks but is still unusual.

Safety and advantages of exercise testing after infarction: Modified treadmill testing at 3 weeks and maximal testing at 8 weeks after acute myocardial infarction under controlled circumstances are more safely performed than unmonitored home activity and are, in fact, desirable in the management and follow-up of patients. The 3rd week exercise test allows assessment before hospital discharge, and the 8th week test allows assessment for return to work or long-term exercise prescription. We found that the 8 week exercise test detected 18 patients (16 percent of the total group of 108) who were in a very high risk group (56 percent) for long-term complications, although their condition had previously been considered uncomplicated. Twenty-five to 29 percent of patients after uncomplicated myocardial infarction who manifested angina or S-T segment depression but were not limited by these signs or symptoms on the 8 week test had a long-term complication. However, exercise-induced S-T elevation did not help to identify patients at risk. Exercise testing allows an objective measure of capacity and, psychological reaction to physical activity as well as of possible myocardial ischemia that would otherwise go unnoticed.

Evaluation of ventricular arrhythmias: Ventricular arrhythmias after acute myocardial infarction are more accurately evaluated with continuous ambulatory monitoring than with exercise treadmill testing.[1] However, more than 600 patients have been studied with exercise to detect arrhythmias in the 2nd and 3rd weeks after acute myocardial infarction. No relation was noted in our study or in that of others between arrhythmia and either angina or S-T segment depression, except in the investigation of Markiewicz et al.[9] In previous studies[3,5,10,12,22] exercise testing detected a 29 to 60 percent incidence rate of premature ventricular complexes after acute myocardial infarction (compared with the 54 percent rate in our study). In our patients, neither the presence, nor the severity of premature ventricular complexes varied significantly from the 3rd to the 8th week after infarction. In other studies,[22,23] their frequency and complexity (in a possibly different type of population) increased between 3 and 12 weeks after acute infarction. A serious arrhythmia observed during exercise after acute infarction denotes a very abnormal response. In our study, patients who manifested premature ventricular complexes that occurred at a rate of more than 30/h on 24 hour ambulatory electrocardiographic recording, were multiform or formed couplets or ventricular tachycardia were treated after the 8th week with long-term propranolol therapy. No sudden deaths were noted in this group of 32 patients.

Prognostic value of exercise testing: Our long-term follow-up findings in patients after acute myocardial infarction extend the data from several other studies in a significant way. It is becoming known that exercise testing after acute myocardial infarction has prognostic value among patients described as free of overt heart failure or chest pain. Our data extend this

group to those with a more truly "uncomplicated" status after acute myocardial infarction, Smith et al.[12] exercised 62 patients to 60 percent of their maximal heart rate 18 days after acute myocardial infarction. Their testing influenced management in 13 patients (21 percent) (administration of antiarrhythmic or antianginal therapy or prolongation of hospitalization). In 20 of the 62 patients S-T depression developed, and in 6 (30 percent) of these either death or reinfarction occurred during a mean 21 month follow-up period, whereas these complications occurred in only 5 percent of patients without S-T segment depression. Such a group of patients who manifest S-T depression at only 60 percent of predicted maximal heart rate show significant ischemia, and this poor prognosis could have been predicted. It seems that a subset of patients, similar to our 18 patients who had a 56 percent incidence rate of complications, were selected.

Theroux et al.[24] studied 210 patients 11 days after acute myocardial infarction with treadmill testing to 70 percent of predicted maximal heart rate. Eighty-three patients were taking propranolol and 22 were taking digitalis. These investigators concluded that exercise testing could predict mortality since only 2.1 percent (3 of 146) of patients without S-T segment changes versus 27 percent (17 of 64) of those with S-T segment depression died in the subsequent year. Sudden death occurred in 1 (0.7 percent) of 146 and in 10 (16 percent) of 64 patients, respectively ($p < 0.001$). It was also significant that angina developed in 65 percent of patients with chest pain during the test but in only 36 percent of those who had no chest pain during the test. These findings also indicate that, similar to our subset of 18 patients, a significant number of their patients had ischemia 2 weeks after infarction. Thus, a clinical evaluation without objective measurements is inadequate to assess which patients are truly at lower risk.

Significant changes from the reference values given for the exercise variables, angina, S-T segment depression and ventricular arrhythmias should be identified early after myocardial infarction. The exercise response of our patients with uncomplicated myocardial infarction should serve as guidelines for recommending exercise prescriptions, antianginal and antiarrhythmic therapy and, possibly, cardiac catheterization.

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Improvement in Ventricular Function During Exercise Studied With Radionuclide Ventriculography After Cardiac Rehabilitation

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A heterogeneous group of 19 consecutive patients with coronary artery disease were studied with radionuclide ventriculography before and after a mean of 6 months of exercise training. Ejection fraction was measured at rest, at matched submaximal supine work loads and during maximal supine bicycle exercise. After training there was no change in mean ejection fraction at rest or during maximal exercise, but a higher maximal mean systolic blood pressure, heart rate and work load were achieved. At equivalent submaximal work loads after training, similar levels of mean heart rate and systolic blood pressure were reached but a statistically greater mean ejection fraction was obtained. These preliminary results suggest that exercise training may improve cardiac function during exercise in selected patients with coronary disease. A randomized study using similar techniques has been initiated.

Improvement in the exercise capacity of patients with coronary artery disease after exercise training has been demonstrated.[1–3] This improvement is associated with peripheral adaptations probably due to circulatory, histologic and enzymatic alterations in the exercised muscle groups, resulting in more efficient function.[4,5] However, few data exist on the effects of training on cardiac function in human subjects, particularly on cardiac function during exertion. No difference was found in ventricular function measured during cardiac catheterization in patients with coronary artery disease before and after exercise training, but these measurements were obtained only during rest.[6–9]

Radionuclide ventriculography provides a simple noninvasive method for the assessment of left ventricular function both at rest and during exercise.[10] The purpose of this investigation was to use radionuclide ventriculography to assess ventricular performance during exercise in patients with coronary artery disease before and after an exercise training program.

Methods

Patient selection: A total of 25 consecutive patients entering our cardiac rehabilitation program who consented to evaluation before and after exercise training were studied. However, six patients were subsequently eliminated: three because the initial studies were conducted less than 3 months after myocardial infarction, two because of necessary changes in medication and one because of mitral regurgitation that made ejection fraction measurements unreliable. Pertinent characteristics of the 19 patients are presented in Table I. The mean age was 51 ± 9 years (range of 35 to 64) and the mean training time was 6 ± 2 months. Four patients had coronary arterial bypass grafting at least 4 months before the initial study. Seven patients were receiving propranolol during this period. The only other medications administrated were nitrates, which were discontinued at least 4 hours before the start of all testing procedures.

Exercise testing: Supine rest and exercise equilibrium radionuclide ventriculography was performed on an imaging table with a mounted electronically

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braked bicycle ergometer (Uniwork-845T, Quinton Instruments) of adjustable height. After acquisition of images at rest, the patient's feet were strapped to the pedals at the 15° elevation. After a brief trial of supine exercise to estimate exercise capacity, exercise testing began at 1/3 the patient's estimated maximal work load. The work load was then increased to approximately 2/3 maximal capacity and finally to the estimated maximal work load. All stages were 3 minutes in duration with scintillation data collected during the last 2 minutes of each stage. Heart rate, blood pressure and the electrocardiogram were carefully monitored and recorded at each stage. Exercise was terminated in most patients at the point of volitional fatigue. However, two patients stopped without symptoms because of 0.3 mV S-T segment depression and four stopped with the onset of definite anginal pain.

Treadmill testing was performed in close proximity (usually 2 weeks) to the radionuclide ventriculographic studies, with use of a modified Balke-Ware protocol.[11] Treadmill speed was 2.0 or 3.3 miles/h with the grade increased 5 percent every 2 or 3 minutes. Termination of the test and acquisition of hemodynamic and electrocardiographic data were the same as for the radionuclide ventriculographic test. Maximal oxygen consumption was estimated from the maximal speed and grade attained, as previously validated.[11]

Equilibrium radionuclide ventriculography: Fifteen to 25 millicuries (mCi) of technetium-99m tagged to human serum albumin was introduced through a catheter in an antecubital vein. Imaging was performed for 5 minutes with the patient supine at rest, and then for 2 minutes during exercise, with use of a modified left anterior oblique camera position with a 10 to 15° caudal tilt. This positioning allowed optimal right and left ventricular and atrioventricular separation. Data were recorded with a mobile single crystal scintillation camera (Picker "Dynamo") equipped with a general purpose parallel hole collimator and processed on a Medical Data Systems PAD computer. The peak of the R wave was used as the physiologic gate. The computer divided the R-R interval into 28 equal time periods (frames) and then assembled data from all of the cardiac cycles in the given acquisition period. The viewer was then able to select the left ventricular region of interest by placing a box around the left ventricle at end-diastole. A computer algorithm based on a combination of the decline of count rate and its second derivative automatically determined the left ventricular border. Generation of a time-activity curve was accomplished by determining the left ventricular counts for each frame corrected for background activity in the left lung. With use of the time-activity curve, ejection fraction (EF) was calculated using the formula: EF = EDC − ESC/EDC, where EDC = left ventricular counts at end-diastole and ESC = left ventricular counts at end-systole. This technique has been validated and shown to be highly reproducible at rest and during exercise in our laboratory.[12,13]

The lowest ejection fraction at rest obtained in our laboratory for a normal person has been 0.53.[14,15] We therefore selected an ejection fraction of less than 0.50 to indicate left ventricular dysfunction at rest. The lowest percent change in ejection fraction (EF) from rest to maximal supine exercise ([exercise EF − rest EF] ÷ rest EF × 100) in normal subjects has been 11 percent. Therefore, we consider any percent change less than this to be consistent with exercise-induced ischemic left ventricular dysfunction.[14,15]

Exercise training program: After the initial treadmill test, an exercise prescription was given with intensities ranging from 65 to 85 percent of the estimated maximal oxygen consumption. Exercise sessions were conducted on Monday, Wednesday and Friday in an electrocardiographic monitored class. The classes consisted of 10 minutes of warm-up, six 5 minute exercise periods on various aerobic exercise devices separated by 2 minute rest intervals, and cool-down activities conducted for an additional 10 minutes. The training activities included treadmill walking, bicycle pedaling, use of an arm ergometers, step climbing, rowing and light lifting.

After completion of monitored training sessions, usually after 3 months, patients were graduated to a walk-jog program either outdoors or in a hospital gymnasium. Warm-up and cool-down activities were similar to those used in the monitored classes. However, aerobic conditioning was accom-

TABLE 1

Characteristics of the Patients

Case	Age (yr)	Training Duration (mo)	Clinical History Before Entering Study
1	60	9	MI 3 months prior, history of angina
2	64	6	MI 2 years prior, atypical chest pain
3	57	6	History of angina, abnormal coronary angiography
4	35	7	MI 4 months prior, abnormal coronary angiography, history of angina
5	58	3	Coronary bypass surgery 7 months prior
6	60	4	MI 7 years prior, abnormal coronary angiography
7	49	4	Mild MI 6 months prior
8	54	4	Markedly abnormal exercise ECG test and risk factors
9	51	3	Abnormal coronary angiography, MI 8 months prior
10	54	3	Small MI 6 years prior, abnormal coronary angiography
11	55	5	MI 1 year prior
12	54	4	Angina, MI 4 years prior
13	60	7	MI 4 years prior
14	38	7	MI 4 months prior
15	41	8	Coronary bypass surgery 4 months prior
16	54	6	Coronary bypass surgery 5 months prior
17	42	9	Coronary bypass surgery 5 months prior
18	49	7	MI 5 months prior, angina
19	37	6	MI 1 year prior
Mean	51	6	
±SD	9	2	

ECG = electrocardiographic; MI = myocardial infarction; SD = standard deviation.

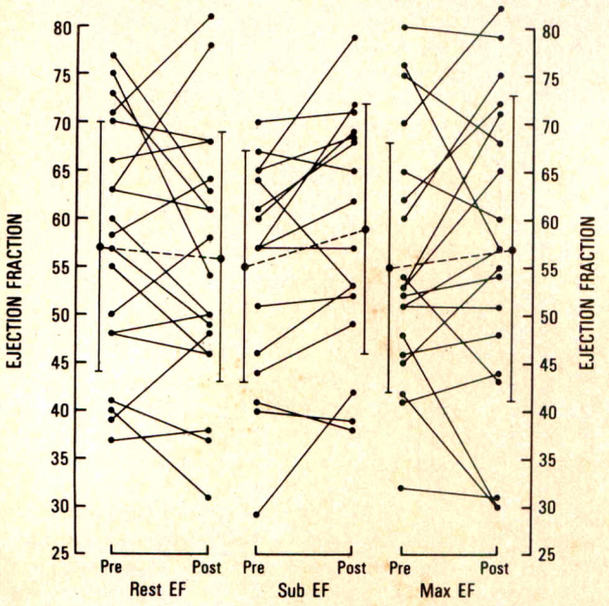


FIGURE 1. Ejection fraction (EF) at rest, at matched submaximal (Sub) work load and at maximal (Max) exercise before (Pre) and after (Post) exercise training.

plished by 30 minutes of continuous walking or jogging, or both. Periodic electrocardiographic, blood pressure and symptomatic assessments were conducted to detect possible contraindications to exercise and to reassess the exercise prescription. No medical complications were observed in any of our patients.

This study was approved by the University of California, San Diego Human Subjects Committee and informed consent was obtained from each patient before any procedures were performed. Statistical testing was done using paired *t* tests.

Results

Resting data (Table II, Fig. 1): There was no change in the mean ejection fraction at rest after exercise training (0.57 ± 0.13 before training versus 0.55 ± 0.13 after training). Of the 19 patients studied, 13 had a normal ejection fraction at rest (0.50 or greater) and 6 had an abnormal ejection fraction at rest. Ejection fractions at rest ranged widely, from a low of 0.31 to a high of 0.81. After training, an abnormal ejection fraction reverted to normal in only one patient and a normal value became abnormal in two patients.

Submaximal exercise data: Scintillation data at matched submaximal work loads were obtained in 16 of the 19 patients before and after exercise training (Tables II and III). We were unable to obtain data at submaximal work loads in three patients because of technical problems. There was no significant difference in the mean submaximal rate-pressure product (product of systolic blood pressure and heart rate) attained during the submaximal work load before and after training ($164 \pm 27 \times 10^2$ versus $164 \pm 33 \times 10^2$). The submaximal systolic blood pressure could not be accurately recorded in one patient before training. The ejection fraction response to these matched submaximal work loads is shown in Table II and Figure 1. After training, there was a significant increase in the mean submaximal ejection fraction (0.55 ± 0.12 before versus 0.59 ± 0.13 after training). Among the 16 patients evaluated at matched submaximal work loads, the ejection fraction increased by 0.04 or more in 8, decreased in 1 and remained unchanged in 7 after exercise training.

Maximal supine bicycle exercise data: The 19 patients demonstrated no significant increase in mean heart rate after exercise training (Table III). However, maximal systolic blood pressure (174 ± 25 before versus

TABLE II

Ejection Fractions Measured Using Radionuclide Ventriculography at Rest and During Supine Bicycle Exercise Before (pre) and After (post) Exercise Training

	Resting EF		Submaximal EF		Maximal EF		% Δ EF	
Case	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0.39	0.48	0.46	0.53	0.46	0.48	+18	0
2	0.57	0.49	0.57	0.62	0.51	0.57	−10	16
3	0.77	0.63	0.65	0.79	0.70	0.82	−10	30
4	0.48	0.50	0.51	0.52	0.51	0.51	+6	+2
5	0.55	0.46	0.44	0.49	0.45	0.55	−18	+14
6	0.60	0.50	0.57	0.57	0.52	0.54	−13	+8
7	0.63	0.61	0.70	0.71	0.75	0.68	+19	+11
8	0.73	0.61	—	—	0.53	0.71	−23	16
9	0.70	0.68	0.61	0.68	0.80	0.79	+14	+16
10	0.66	0.68	0.67	0.65	0.54	0.43	−18	−37
11	0.40	0.31	0.41	0.38	0.42	0.30	+5	−3
12	0.48	0.46	0.40	0.39	0.48	0.30	−2	−40
13	0.63	0.78	—	—	0.60	0.75	−5	−4
14	0.41	0.37	—	—	0.41	0.44	0	+19
15	0.75	0.54	0.64	0.53	0.76	0.57	0	+5
16	0.58	0.64	0.57	0.72	0.62	0.72	+7	+13
17	0.50	0.58	0.60	0.69	0.54	0.65	+8	12
18	0.71	0.81	0.65	0.68	0.65	0.60	−8	−24
19	0.37	0.38	0.29	0.42	0.32	0.31	−14	−18
Mean	0.57	0.55	0.55	0.59	0.56	0.56	−2.3	2.5
±SD	0.13	0.13	0.12	0.13	0.13	0.16	13	19
p	NS		<0.05		NS		NS	

EF = ejection fraction; NS = not significant; p = probability; SD = standard deviation; %ΔEF = mean percent change in ejection fraction.

184 ± 24 after training) and rate-pressure product (223 ± 57 × 10^2 before versus 246 ± 69 × 10^2 after training) were significantly increased after training. In addition, the patients attained a greater mean maximal work load after the training program (661 ± 172 kpm before versus 768 ± 229 kpm after training). In 13 patients the peak work load increased after training; in 5 it remained unchanged and in only 1 it decreased.

The mean maximal ejection fraction did not change after exercise training (0.56 ± 0.13 before versus 0.56 ± 0.16 after training) at the higher mean rate pressure product and work load (Tables II and III). Maximal ejection fraction increased by 0.04 or more in seven, decreased in six and did not change in six after exercise training.

Change in ejection fraction from rest to maximal exercise: The increase in the mean percent change in ejection fraction from rest to maximal supine bicycle exercise was also not significant (−2.3 ± 13 percent before versus 2.5 ± 19 percent after training) (Fig. 2, Table II). In 11 patients the percent change in ejection fraction increased and in 8 it decreased after exercise training. However, if a normal response to supine bicycle exercise was considered to be a percent change of 10 percent or more, the ejection fraction response to supine bicycle exercise after exercise training normalized in 7 patients, remained unchanged in 11 and became abnormal in only 1. All seven patients whose ejection fraction response normalized showed an increase in absolute maximal ejection fraction after training, but some of them also showed a decrease in ejection fraction at rest. Among the 12 patients whose ejection fraction response did not normalize (there was no change in 11 and in 1 the response became abnormal after training),

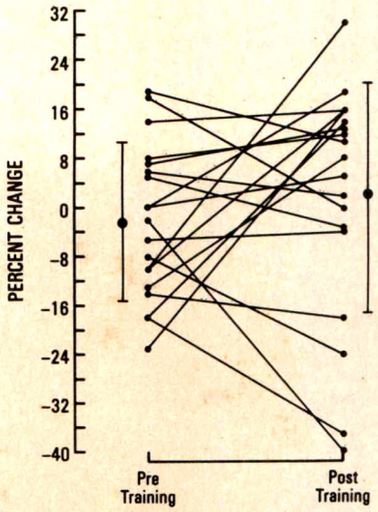


FIGURE 2. Percent change in ejection fraction from rest to peak exercise before (Pre) and after (Post) exercise training.

10 attained either a greater rate-pressure product or a greater maximal work load after training. Seven of these 10 patients attained both higher values for both rate-pressure product and work load after training.

Treadmill test data (Table IV): The training effect of the exercise program was evaluated by comparing mean heart rate, systolic blood pressure, rate-pressure product and estimated maximal oxygen consumption with treadmill tests performed before and after the training program. A training effect was demonstrated by a significant increase in mean estimated maximal oxygen consumption (31 ± 8 before versus 37 ± 9 cc/

TABLE III

Maximal Work Loads, Heart Rate (HR), Systolic Blood Pressure and Rate-Pressure Product in Response to Supine Bicycle Exercise Before (pre) and After (post) Exercise Training

	Maximal Work Load (kpm)		Maximal HR		Maximal SBP		Maximal RPP		Submaximal RPP*	
Case	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	400	600	110	119	148	156	163	186	158	153
2	600	800	120	125	180	196	216	245	155	168
3	600	600	108	105	185	200	200	210	—	342
4	500	600	85	88	150	148	128	130	128	111
5	400	500	107	103	150	156	161	161	140	132
6	600	400	125	115	164	172	205	198	179	198
7	800	1200	170	166	180	210	306	349	173	176
8	800	800	160	142	182	176	291	250	—	—
9	600	600	125	114	186	170	233	194	188	146
10	800	1000	131	150	220	230	288	345	181	171
11	600	800	135	174	188	205	254	357	176	205
12	400	400	97	94	120	165	116	155	110	139
13	750	900	135	132	175	160	236	211	—	—
14	900	1000	127	162	190	180	241	292	—	—
15	700	900	126	148	140	170	176	252	145	143
16	500	600	102	112	200	230	204	258	155	139
17	800	1000	145	140	215	185	312	259	212	154
18	900	900	152	145	165	190	251	276	198	221
19	900	1000	155	170	165	200	256	340	173	215
Mean	661	768	127	132	174	184	223	246	164	164
±SD	172	229	23	26	25	24	57	69	27	33
p	<0.005		NS		p <0.05		p <0.05		NS	

* Values for submaximal rate-pressure product (RPP) are at matched work loads.
RPP = rate-pressure product (RPP = HR × SBP × 10^2); SBP = systolic blood pressure.

TABLE IV
Demonstration of Training Effect by Comparison of Estimated Maximal Oxygen Consumption, Heart Rate, Systolic Blood Pressure and Rate-Pressure Product at a Submaximal Work Load of 3.3 Miles/Hour at 5 Percent Grade

	Est. $\dot{V}O_2$ max (cc/kg-min)		Submax RPP ($\times 10^2$)		Submax HR		Submax SBP	
Case	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	24	30	156	143	120	110	130	130
2	28	44	180	157	120	108	150	145
3	28	28	166	158	107	100	155	158
4	34	38	123	123	88	88	140	140
5	20	28	200	180	119	120	168	150
6	30	36	174	188	129	125	135	150
7	64	54	253	166	136	120	186	138
8	44	40	—	150	108	100	—	150
9	30	28	—	—	—	—	—	—
10	30	30	260	152	130	98	200	155
11	28	44	156	188	120	125	130	150
12	22	20	137	130	105	100	130	130
13	20	36	—	180	—	100	147	180
14	36	38	157	169	131	126	120	134
15	36	44	182	174	130	120	140	145
16	28	36	269	195	125	93	215	210
17	44	44	205	161	130	115	158	140
18	28	34	238	205	140	130	170	158
19	44	52	185	147	122	115	152	128
Mean	31	37	190	165	121	111	154	150
±SD	8	9	44	23	13	13	26	20
p	$p < 0.001$		< 0.05		< 0.001		NS	

Est. $\dot{V}O_2$ max = estimated maximal oxygen consumption; Submax = submaximal; other abbreviations as in Table III.

kg-min after training), a lower mean rate pressure product ($190 \pm 44 \times 10^2$ before versus $165 \pm 23 \times 10^2$ after training) and a lower mean heart rate (121 ± 13 before versus 111 ± 13 after training) at a matched submaximal treadmill speed and grade.

Discussion

Experimental documentation of cardiac effects of exercise training: Animal studies[16,17] have provided strong evidence supporting the hypothesis that left ventricular function can be improved with exercise training. Bersohn and Scheuer[18] studied the effects of long-term exercise on the rat heart. Exercised rats and control rats were killed and their hearts perfused under aerobic and ischemic conditions. Coronary blood flow was reduced by 40 percent to produce ischemia, and measurements were made in both trained and untrained rat hearts at equivalent levels of myocardial oxygen consumption. Increased left ventricular pressure, a 30 percent greater stroke volume, prolonged diastole and faster relaxation were reported for hearts of exercise-trained rats during ischemic conditions. Under normal conditions, the trained rat hearts exhibited a longer diastolic phase and faster relaxation than did the untrained rat hearts. In another study,[19] these investigators demonstrated enhanced ejection fraction, circumferential fiber work, cardiac output and stroke work in trained rats. Improved myocardial contractility has also been shown[20] to occur in dogs after exercise training by plotting the first derivative of ventricular pressure (dP/dt) as a function of heart rate. Although not all animal studies have found augmented left ventricular function after exercise training,[21] most studies have shown that on a long-term basis exercised young animals demonstrate enhanced cardiac function.

Echocardiographic assessment of effects of exercise training: Echocardiography has been used to assess the effects of training on chamber size, left ventricular wall thickness and resting left ventricular function in human subjects. Longitudinal studies comparing echocardiographic measurements made before and after training have yielded conflicting results. Ehsani et al.[22] reported a rapid increase in left ventricular volume and mass in healthy young adults after a swimming program. These dimensional changes occurred in less than 5 weeks, but no changes were found in the ejection fraction at rest. DeMaria et al.[23] found similar results including increases in left ventricular end-diastolic dimension, stroke volume and shortening fraction after exercise training in 24 healthy adults. Using radionuclide ventriculography, Sheps et al.[24] found in six normal men an increase in ejection fraction at rest at the same basal heart rate after training. Stein et al.[25] were the only investigators to study training-induced changes in ejection fraction during semisupine exercise using echocardiography and found that ejection fraction increased in healthy college students after an exercise program. Wolfe et al.[26] studied middle-aged men and found a moderate increase in stroke volume at rest due to an increase in end-diastolic dimension secondary to a longer ventricular filling time. However they found no change in left ventricular structure or resting contractile state. Other investigators[27–29] have also been unable to document morphologic or functional changes. Most echocardiographic studies[30–32] comparing athletes with sedentary subjects have found no significant difference in left ventricular function at rest

The inconsistencies in these studies demonstrate the difficulty in finding changes in ventricular function or dimensions after exercise training. This is particularly the case in older subjects and when using low levels of training.

Other clinical physiologic studies in exercise training: A controlled study examining cardiovascular adjustments accompanying exercise training in patients after myocardial infarction was recently conducted by Paterson et al.[33] These investigators randomly assigned 79 patients to an exercise group of either high or low intensity and followed them up for 1 year. During exercise testing, they found an augmented arteriovenous oxygen difference at 6 months and an increase in stroke volume at 12 months in the high intensity group only. The early study of Frick[34] also found improved exercise stroke volume in patients undergoing exercise training. The increased exercise stroke volume in these two studies suggests cardiac adaptations to long-term exercise and illustrates the importance of evaluating changes during exertion rather than at rest.

Data obtained during cardiac catheterization using contrast ventriculography[6–9] have shown no change in left ventricular regional or global function at rest in patients with coronary artery disease before and after exercise training. These angiographic studies have used left ventricular ejection fraction as the best means of evaluating the contractile performance of the heart at rest. Such studies are difficult to perform during exercise because of technical difficulties in adequately opacifying the ventricular cavity.

Left ventricular function after training studied with radionuclide angiography: The use of radionuclide ventriculography made it possible to assess noninvasively the response of left ventricular ejection fraction not only at rest but also during exercise in our 19 patients. Consistent with previous results utilizing cardiac catheterization,[6–9] no significant change in mean resting ejection fraction was found in our patients after training. When radionuclide ventriculography was used in patients before and after coronary arterial bypass grafting, ejection fraction at rest was not changed.[35]

The contractile state of the heart during equivalent submaximal exercise was assessed in 16 of our 19 patients who performed the same submaximal work load during supine bicycle exercise before and after training. There was a significant increase in submaximal ejection fraction after training. This occurred at the same level of myocardial oxygen demand, as reflected by rate-pressure product,[36] and at the same bicycle work load. Submaximal ejection fraction before and after training has not previously been studied. However, in patients who had clinical improvement after coronary arterial bypass grafting, Kent et al.[35] demonstrated increased ejection fraction and fewer exercise-induced wall motion abnormalities at the same work load as that performed preoperatively.

There was no reduction in heart rate or systolic blood pressure at matched submaximal supine bicycle work loads after training. These findings could be due either to the specificity of training (because patients were tested in the supine position but were exercised in the erect position only) or to positional ventricular volume differences.

Mean ejection fraction obtained at maximal exercise showed no change after exercise training. An increase in ejection fraction at maximal work load was inhibited by the greater myocardial oxygen demand reflected by the higher maximal rate-pressure product and work load attained after training. There was also no significant increase in the mean percent change in ejection fraction from rest to maximal exercise after training. However, in seven of our patients this ejection fraction response normalized and in only one did it become abnormal after the exercise training program. We were careful to eliminate from the investigation patients who were initially studied less than 3 months after myocardial infarction as well as those who had mitral regurgitation or required medication that might affect the exercise tests. We have noticed spontaneous improvement in ejection fraction in patients as they recover from a myocardial infarction or while they are taking nitroglycerin or propranolol, or both.[37,38]

Correlation with clinical state: Our study group is heterogeneous because of the small number of consecutive patients studied and the types of patients that present to an outpatient exercise program. For this reason we were unable to detect trends in the data relating the ejection fraction responses to clinical information or other exercise test responses. Attempts at multivariate analysis resulted in too few subjects in each classification to make meaningful conclusions.

Four patients joined our program after coronary bypass grafting. There was no significant change in their mean (0.57 before versus 0.55 after training) ejection fraction or peak (0.59 before versus 0.62 after training) exercise ejection fraction at rest, but three of the four patients had an increase in submaximal ejection fraction. This change, together with an increase in estimated maximal oxygen consumption (32 cc O_2/kg-min before versus 38 after training), support the conclusion of Oldridge et al.[39] that exercise training can be beneficial to patients after coronary bypass surgery. Our observations are also consistent with those of Paterson et al.,[33] who were unable to correlate improved exercise stroke volume after training to initial or final clinical status. In addition, Lee et al.[40] found no correlation between increased work capacity and left ventricular function after exercise training.

Bruce et al.[41] used invasive techniques before and after exercise training to study 10 patients with coronary disease. Although the condition of all was improved, some of the patients showed a definite decline in exercise cardiac output and stroke volume, a deterioration that could have been secondary to progression of disease or to their exercise program. This finding points out the need to develop noninvasive techniques to identify such patients.

Rate-pressure product has been demonstrated to be an accurate estimate of myocardial oxygen demand during exercise.[36] Because it is doubtful that there would be a decrease in end-diastolic volume after training in these patients, the ejection fraction response may reflect an adaptive increase in left ventricular

contractility at the same or a greater myocardial oxygen consumption, improvement in myocardial microcirculation or reduced coronary flow requirements. Therefore, it appears that, like peripheral muscle, cardiac muscle may become more efficient after training. Future exercise training studies need to include measurement of left ventricular volume[42] and other measures of ventricular contractility[43] and to include assessment of myocardial perfusion.[44,45]

Clinical implications: Concomitant with the peripheral adaptations demonstrated in patients with coronary artery disease responding to exercise training, selected patients may also demonstrate augmented left ventricular function during exercise. However, reports[44,45] have emphasized the importance of considering spontaneous improvement in function after a myocardial infarction. For this reason, randomized larger studies considering left ventricular function and perfusion, exercise capacity, severity of disease and clinical status are needed to document our preliminary findings and to assess which patients respond most favorably to exercise training as a mode of therapy. Perhaps even those who are likely to have an adverse hemodynamic response can be identified. Currently at this institution such a study, called PERFEXT (an acronym for perfusion and performance exercise trial), is being sponsored by the National Institutes of Health, Bethesda, Maryland.

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Relation of Exercise-Induced Physiologic S-T Segment Depression to R Wave Amplitude in Normal Subjects

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Exercise electrocardiography was performed in 100 asymptomatic male volunteers with a mean age of 42.6 years. The R wave and total RS amplitude and the magnitude of physiologic S-T segment depression at the J junction were quantitated for a modified bipolar CC_5 lead and a vertically oriented bipolar lead (VL) using computer-averaged groups of 25 consecutive QRS complexes from each of seven stages of rest and exercise. Computer-generated X-Y plots were used to examine the correlations between the magnitude of S-T depression and the R wave and total RS amplitudes. The magnitude of S-T depression and of the R wave amplitude were unrelated at standing rest but showed increasing correlation with progressive increases in exercise heart rate (correlation coefficient = 0.425, $p < 0.00001$ at maximal exercise). The total RS amplitude was also related to the magnitude of S-T depression during exercise, but the correlations did not improve progressively with increases in exercise heart rate. The magnitude of S-T depression was more closely related to R wave amplitude and total RS amplitude in the vertically oriented lead than in the CC_5 lead.

These data demonstrate a significant relation between the magnitude of R wave and total RS amplitudes and the magnitude of physiologic S-T segment depression in normal subjects during exercise. They suggest the need for evaluation of S-T depression corrected for R wave amplitude in an attempt to improve the diagnostic accuracy of the exercise electrocardiogram. The data also suggest that the criteria for abnormal S-T depression should take into consideration the different R wave voltages reflected by different types of recording leads.

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The clinical utility of the diagnostic exercise electrocardiogram is fundamentally based on changes that occur in the S-T segment in response to increasing work loads and heart rates. The depth of S-T segment depression is one of the measurements used to identify patients with clinically significant coronary artery disease. In normal subjects some degree of depression is usually seen in the early portions of the S-T segment during exercise, and the clinical differentiation between a normal and an abnormal response largely depends on the magnitude and contour of the S-T depression. The mechanisms and correlates of physiologic S-T depression in normal subjects have not been clearly established. The purpose of this study was to determine whether a relation exists between the electrocardiographic R wave amplitude and the degree of exercise-induced S-T segment depression during exercise in normal subjects.

Methods

Study subjects: The study group consisted of 100 asymptomatic and presumably healthy male members of the Indiana State Police Force. The mean age was 42.6 years (range 32 to 55). No study subject was receiving antiarrhythmic drugs, propranolol or a digitalis glycoside, and none had diastolic blood pressure of 90 mm Hg or more at rest. All subjects had a normal 12 lead electrocardiogram at rest and none demonstrated S-T segment depression on the bipolar monitor leads before exercise.

Exercise test protocol: Treadmill exercise was performed with use of a modified Balke protocol.[1] The exercise electrocardiogram was continuously monitored using a modified bipolar CC_5 lead and a vertically oriented bipolar lead (VL) that simulates lead II of the standard electrocardiogram. Placement of the exploring electrode for the modified CC_5 lead varied from the V_4 to V_6 position in any given subject so as to obtain a maximal R wave amplitude. However, care was taken to choose an electrode position that also yielded a complex with a small S wave.[1] The exploring electrode for the bipolar vertical lead was placed at the lower left costal margin in the mid axillary line and the corresponding negative electrode was placed on the forehead. All exercise tests were performed under the direct supervision of a physician and were terminated when the subjects reached their symptom-limited work load. No subject experienced chest pain. The maximal heart rates achieved ranged from 142 to 214 beats/min; the mean maximal heart rate was 177.5 beats/min. All but one subject achieved greater than 85 percent of his age-predicted maximal heart rate.

Analysis of exercise test data: The exercise electrocardiogram was continuously recorded on magnetic tape using a Hewlett-Packard 3964A recorder. A time code was simultaneously generated and recorded on one channel of the tape recorder so that selected intervals of the electrocardiographic data could be subsequently located for computer averaging.[1] For this study 25 consecutive QRS complexes were selected from the period of standing rest, from two submaximal exercise periods (heart rates approximately 120 and 140 beats/min, respectively), from maximal exercise, from the onset of recovery and from the 3 and 6 minute recovery periods. The analog data were converted to a digital format at a frequency of 500 samples/s and a Data General Corporation Nova 2–10 computer was used for computer-averaging of the QRS complex.[1] The computer was programmed to locate the peak of the R wave of the averaged QRS complex, and an isoelectric interval was then identified within the 35 data points (70 ms) preceding that peak. The isoelectric interval, defined as the 10 ms interval with the least slope, served as the baseline for computation of the R wave amplitude in millivolts (Fig. 1). The 10 ms interval in the S-T segment starting at 60 ms beyond the peak of the R wave was used to compute the S-T level in millivolts relative to the isoelectric interval. The nadir of the S wave was identified as the most negative point in the averaged QRS complex occurring within a 40 ms interval after the peak of the R wave, and the total RS amplitude was computed in millivolts using this point and the R wave peak (Fig. 1).

Six patients had significant widening of the QRS complex during exercise that resulted in erroneous computer localization of the S-T segment interval within the terminal QRS complex. These six subjects, identified through the plots of the averaged QRS complexes, were omitted from the study.

Statistical analysis: The relation of R wave amplitude to the magnitude of computer-averaged S-T segment depression was then graphically plotted for the study group of 94 subjects for each of the seven stages of rest, exercise and recovery. Figure 2 shows a representative plot of physiologic S-T depression versus R wave amplitude recorded in the vertical lead during maximal exercise. A correlation coefficient (r value) was computed for each plot, and the significance of the relation between the R wave amplitude and the magnitude of S-T depression for each stage of exercise was assessed using the test for significance of correlation coefficients. Similar plots and data analyses were generated correlating the total RS amplitude to the magnitude of S-T depression for each stage of exercise.

Results

Correlation of R wave amplitude and S-T depression (Table I): Figure 3 shows a series of correlation coefficients (r) relating the electrocardiographic R wave amplitude to the magnitude of S-T segment depression in the two recorded leads at various stages of rest and exercise. At standing rest, the correlation coefficient between R wave amplitude and the magnitude of S-T depression was small and not statistically significant in either lead. With exercise, a statistically significant relation existed for all stages of exercise and recovery between the R wave amplitude and the magnitude of S-T depression in both leads. In the CC_5 lead the relation became significant at a heart rate of 120 beats/min and the r value increased progressively with increasing heart rates, reaching 0.425 at maximal exercise. The relation between R wave amplitude and S-T depression in the CC_5 lead during maximal exercise was described by a slope of −0.36 and an intercept of 1.3. The significant relation between these variables in lead CC_5 continued during the 3 and 6 minute recovery periods. In the vertically oriented lead there was a significant correlation between the two variables at an exercise heart rate of 120 beats/min (Fig. 3). This correlation increased with progressive exercise, the r value becoming 0.564 at maximal exercise (slope −0.57, intercept 2.1). Correlation coefficients during all stages of exercise and recovery periods were statistically significant ($p < 0.001$).

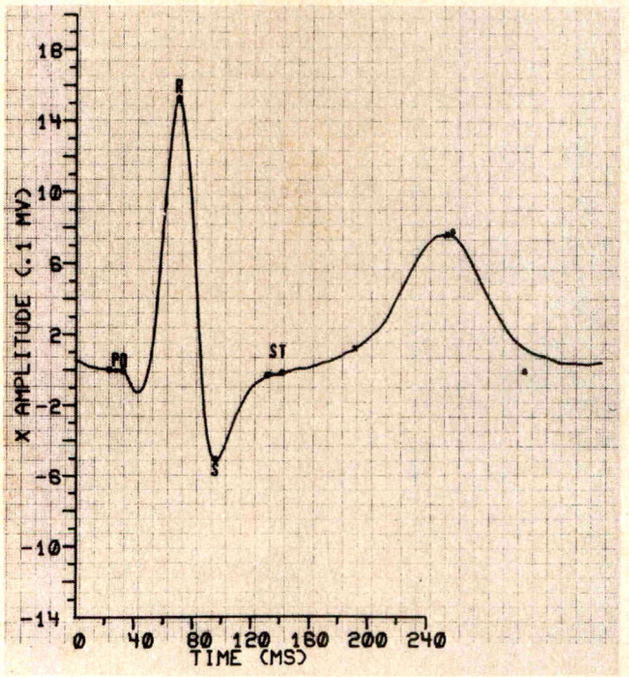


FIGURE 1. Electrocardiographic QRS as derived by computer-averaging of 25 complexes. Sample reference points for the calculation of electrocardiographic wave amplitudes are demonstrated. MS = milliseconds; MV = millivolts; PQ = 10 ms isoelectric interval; R = peak of R wave; S = nadir of S wave; ST = 10 ms interval for measurement of S-T level.

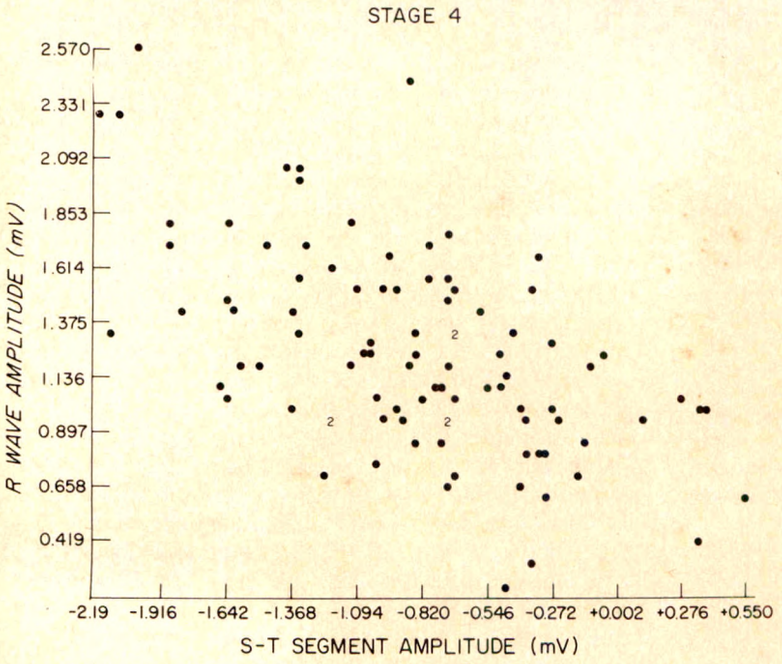


FIGURE 2. Scattergram demonstrating the magnitude c physiologic S-T segment depression versus the magni tude of R wave amplitude in the vertical lead durin maximal exercise (stage 4)

Correlation of total RS amplitude and S-T depression (Table I): Figure 4 illustrates a series of correlation coefficients for the different stages of rest and exercise correlating the total RS amplitude with the magnitude of S-T segment depression. At standing rest there was no significant relation between the RS amplitude and the magnitude of S-T depression in the CC_5 lead. A weak relation was present in the vertical lead ($r = 0.179$, $p < 0.05$) at standing rest. With exercise, the S-T depression was significantly related to the RS amplitude in both leads at all stages of exercise and recovery. Unlike the correlation of R wave amplitude to S-T depression, the relation between the total RS amplitude and the magnitude of S-T depression did not increase progressively as the exercise heart rate increased.

Discussion

S-T segment depression during exercise in normal subjects: The major variable of measurement ir diagnostic exercise electrocardiography is the magni tude of depression of the S-T segment. However, S-T depression also occurs in normal subjects during exercise,[2] a finding that often limits the diagnostic speci ficity of the exercise electrocardiogram. The problem of S-T depression in normal subjects is generally ap proached by considering the slope or rate of rise of the S-T segment. The S-T depression observed in norma subjects during exercise is thought to be in part due to an increase in the magnitude of the atrial repolarization wave (Ta wave)[3] combined with shortening of the QRS interval,[4] and the J point and initial portion of the S-T segment are primarily altered. These physiologic al

TABLE I

Mean Values (mV) of R Wave Amplitude, RS Amplitude and S-T Segment Depression During Seven Stages of Rest, Exercise and Recovery in 94 Subjects

		Submaximal Heart Rate			Recovery		
	Standing Rest	120 Beats/ Min	140 Beats/ Min	Maximal Exercise Heart Rate*	Immediate	3 Min	6 Min
CC5 lead							
Mean R wave amplitude	1.88	1.90	1.85	1.62	1.43	1.82	1.82
Mean RS amplitude	2.26	2.39	2.42	2.37	2.25	2.42	2.35
Mean S-T depression	0.25	−0.35	−0.71	−0.78	− 34	−0.28	−0.34
Vertical lead							
Mean R wave amplitude	1.43	1.41	1.41	1.27	1.16	1.56	1.56
Mean RS amplitude	1.61	1.69	1.73	1.68	1.60	1.87	1.83
Mean S-T depression	0.39	−0.31	−0.74	−0.85	− 53	−0.24	−0.28

* Mean 178 beats/min.

terations result in upsloping S-T depression that can usually be differentiated from the more horizontal or even downsloping S-T depression of exercise-induced myocardial ischemia. Consideration of the S-T segment slope has proved useful in the clinical interpretation of S-T depression, but the occurrence of depressed S-T segments in normal subjects remains a problem, especially when one attempts to apply slow upsloping S-T segment criteria.[5,6] Further understanding of the electrocardiographic correlates of exercise-induced S-T depression in normal subjects may prove helpful in separating normal from abnormal S-T segment responses.

Correlation of R wave amplitude and magnitude of S-T depression during exercise in normal subjects: Blackburn et al.[7] found no significant correlation between the amplitude of the R wave (lead CM_5) and the magnitude of S-T segment depression at rest in patients with heart disease. Our study found a similar lack of correlation between these two in normal subjects at rest, although there was a direct relation between the magnitude of S-T depression and the amplitude of the R wave during exercise in these subjects. The correlation between R wave amplitude and the magnitude of S-T depression increased progressively with increasing heart rates up through maximal exercise. When the total RS amplitude was compared with the magnitude of S-T depression for each stage of exercise, a lesser correlation was observed, and the correlation was not enhanced as the heart rate during exercise increased. The depth of the S wave progressively increases during increasing levels of exercise in normal subjects[8,9] (Table I), and it is possible that the relation between the S wave and the S-T segment vectors is the reverse of that of the R wave and these vectors.

Other factors influencing magnitude of S-T depression during exercise: Our study demonstrates that the magnitude of the S-T segment depression during exercise is related to the R wave amplitude in normal subjects. However, the correlation coefficients are relatively weak and other independent factors obviously influence the depth of S-T depression. One factor that may limit the correlation between R wave amplitude and S-T depression is the decrease in R wave amplitude that occurs in normal subjects during exercise.[8–10] The greatest decrease in R wave amplitude occurs at or near maximal exercise at a time when the S-T depression is greatest (Table I). The correlation coefficients could also have been adversely influenced by our computer quantitation program, which uses a fixed 10 ms interval starting at 60 ms after the peak of the R wave to compute S-T depression. As the QRS complex narrows in response to exercise,[4] this interval will be displaced further into the S-T segment; depending on the rate of rise or slope of the S-T segment, the computed S-T depression may be significantly less than the value that would be obtained if all measurements were made in the same area of the proximal S-T segment.

Role of different electrocardiographic lead systems: In our study the R wave and the S-T segment

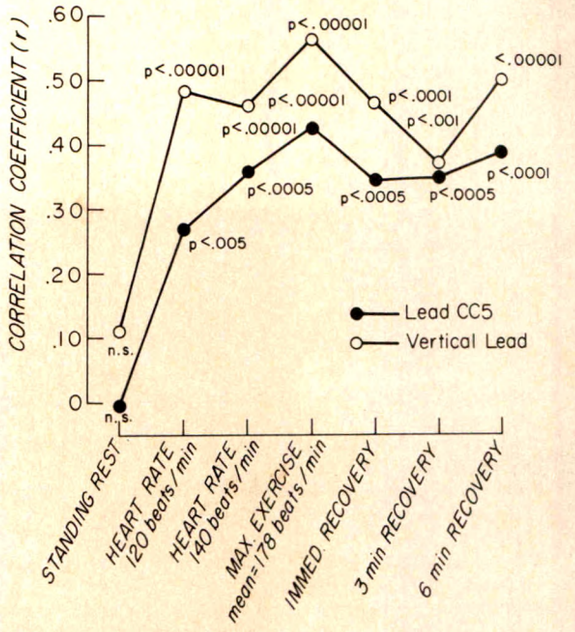


FIGURE 3. Correlation coefficients relating R wave amplitude to the magnitude of S-T segment depression at different stages of exercise. IMMED. = immediate; MAX. = maximal; n.s. = not significant; p = probability.

were more closely related in the vertical lead than in the modified CC_5 lead. A more vertically oriented bipolar V_5 lead such as CM_5 might also demonstrate a closer relation between the R wave amplitude and the magnitude of S-T segment depression than lead CC_5 because the R wave amplitude is taller in lead CM_5.[11] Computer quantitation studies by Froelicher et al.[11]

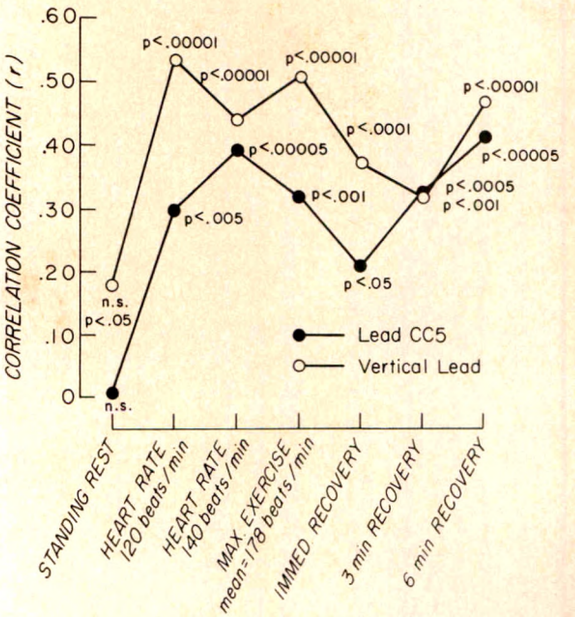


FIGURE 4. Correlation coefficients relating R wave amplitude plus S wave depth to the magnitude of S-T segment depression at different stages of exercise. Abbreviations as in Figure 3.

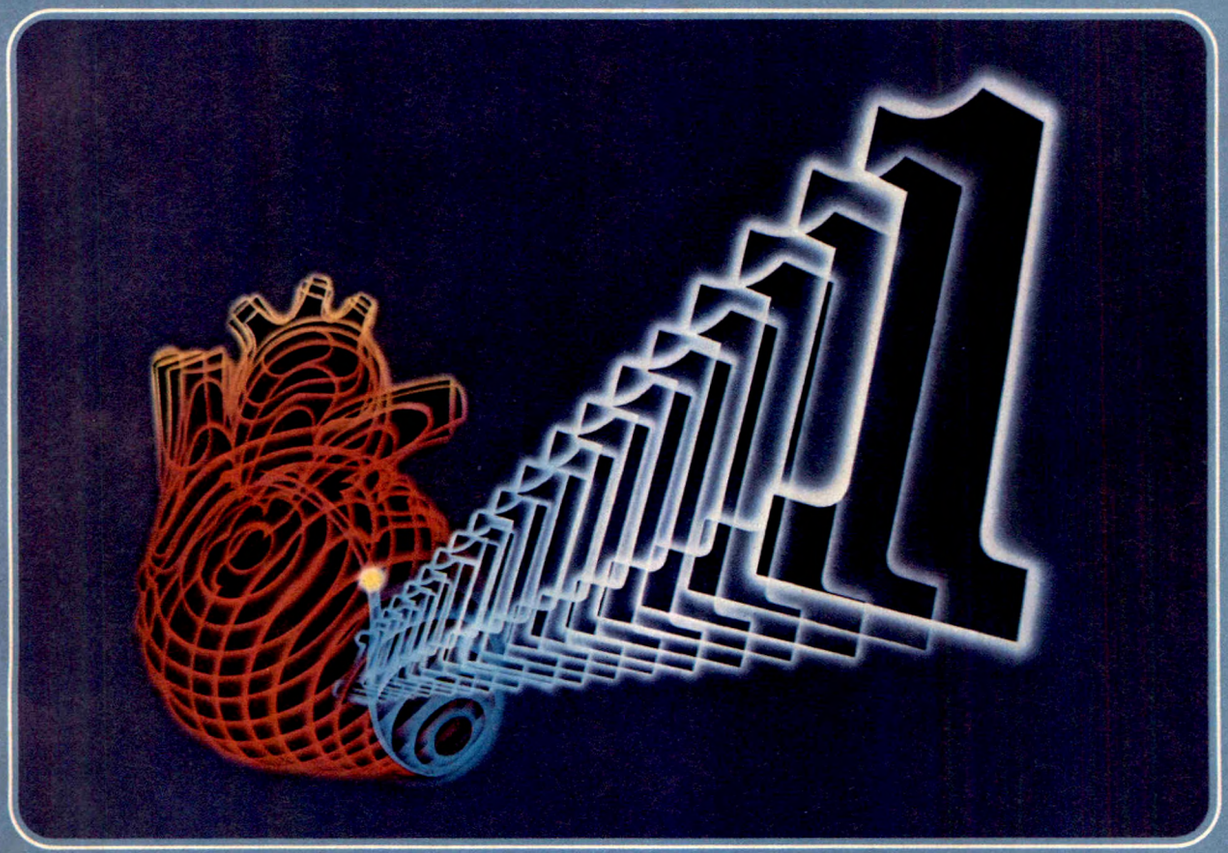
found that the magnitude of S-T depression was greater in lead CM_5 than in leads V_5 or CC_5 in the postexercise period in patients with abnormal S-T segment responses to exercise. They suggested that different criteria may have to be defined for different electrocardiographic leads if repolarization changes in these leads are to have comparable diagnostic significance.

Implications: By demonstrating a significant relation between the amplitude of the R wave and the magnitude of physiologic S-T segment depression during exercise, our study raises the possibility that the sensitivity and specificity of the exercise electrocardiogram can be improved by correcting the amount of S-T depression for the magnitude of R wave amplitude. The study also suggests the need to modify the criteria for abnormal S-T depression depending on the type of lead system used and the magnitude of the R wave reflected in that lead.

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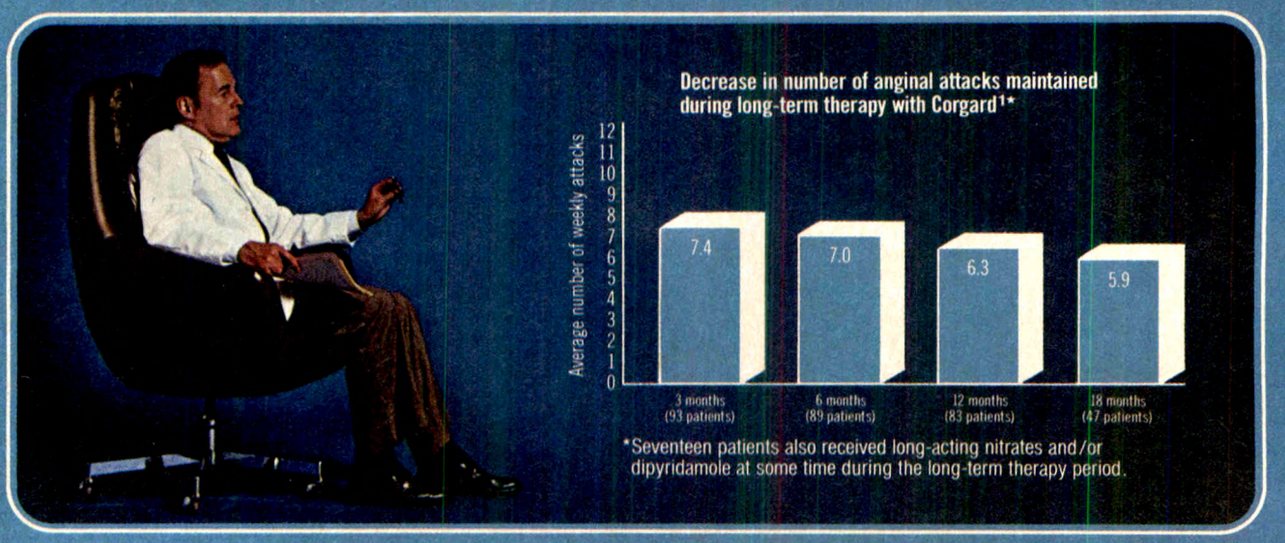


The first and only beta-blocker with once-a-day dosage

In the treatment of angina pectoris

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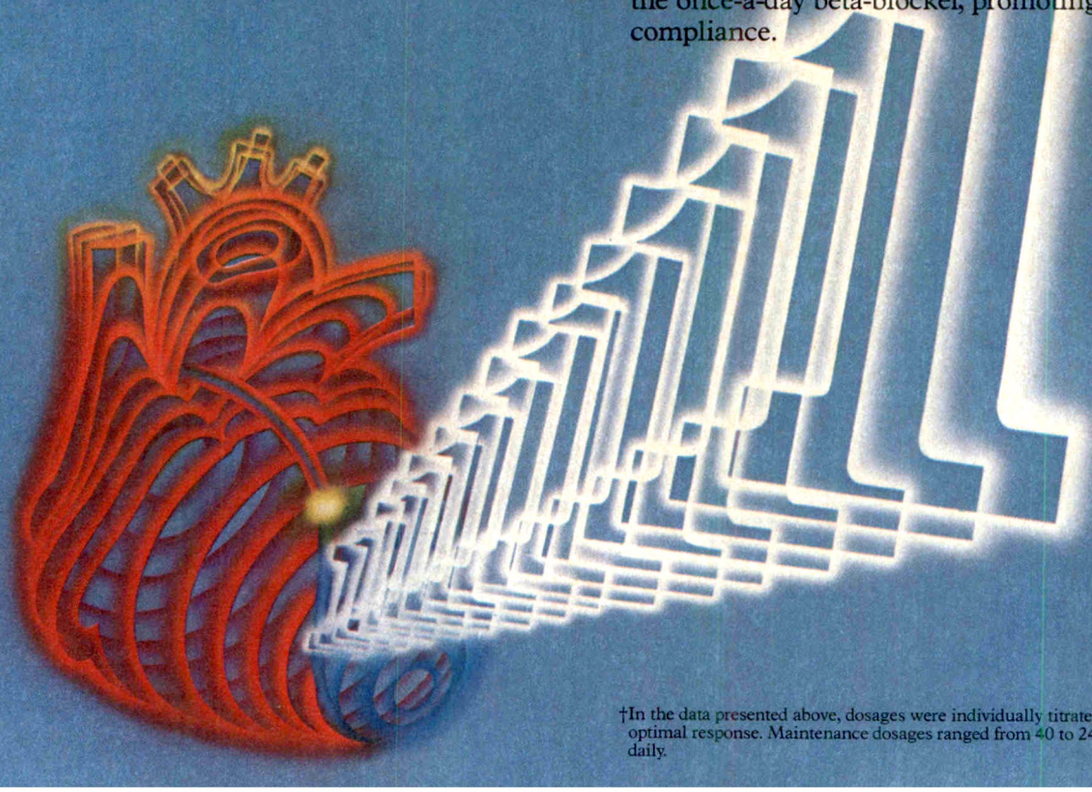
CORGARD® [nadolol tablets]:

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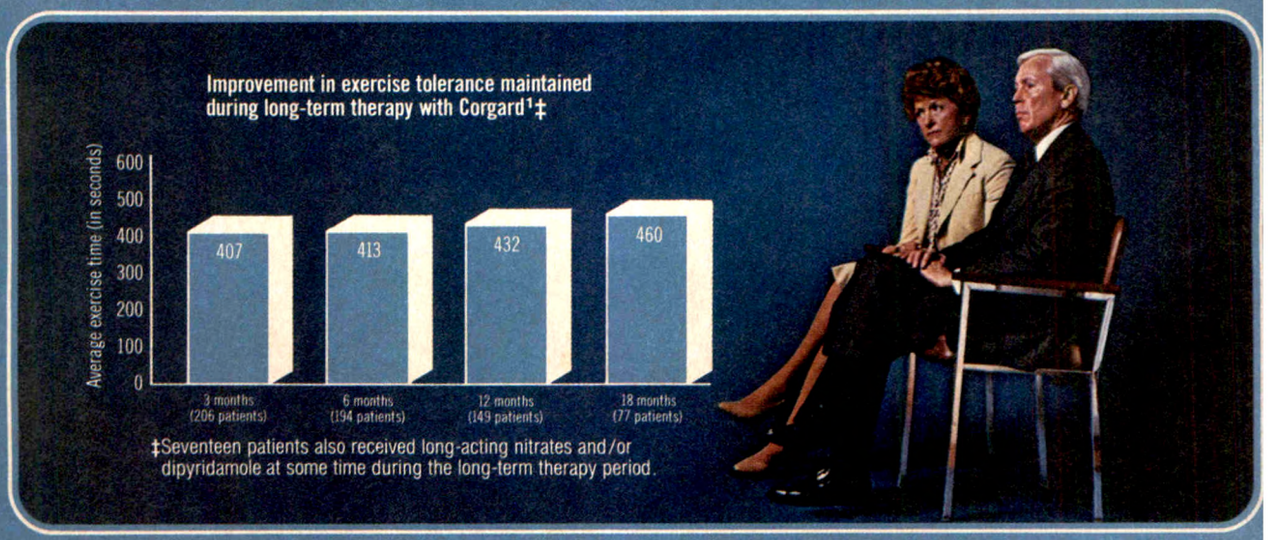
A single daily dose of Corgard offers prophylaxis in angina pectoris, helping to protect the patient all day and all night from painful attacks. And in extended clinical studies, the efficacy of Corgard — as demonstrated by a decreased rate of anginal attacks and an increase in exercise tolerance — was maintained.[1]

Once-a-day, everyday, Corgard decreases the frequency of anginal attacks

Corgard taken just once daily offers round-the-clock protection from angina pain. In one short-term study, Corgard, once a day, decreased the average number of anginal attacks per week in 115 patients with angina, from 13.6 pretherapy to 6.4 at the end of 14 weeks of therapy, a mean decrease of 59%.[1†] In 19% of the 115 patients, anginal attacks were completely eliminated. And the long half-life (20 to 24 hours) makes Corgard the once-a-day beta-blocker, promoting patient compliance.



†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



Effective control of angina pectoris

Once-a-day, everyday, Corgard increases exercise tolerance

Corgard allows the angina patient to do more. In 147 patients in the same short-term study as the one at left, Corgard, once a day, increased ergometry time by 25%, improving exercise tolerance from an average of 365 seconds pretherapy to 427 seconds at the end of 14 weeks of therapy.[1] In 21% of the 147 patients, the end point of exercise was fatigue rather than angina pain. And the single daily dose of Corgard can be taken at the patient's convenience, without regard to meals.

Once-a-day, everyday, Corgard decreases nitroglycerin usage[1]

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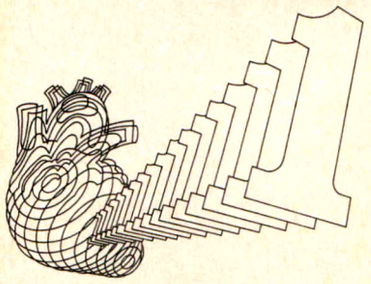
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The common-sense beta-blocker for angina pectoris

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Effective control of angina pectoris... and hypertension



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Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, or 120 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

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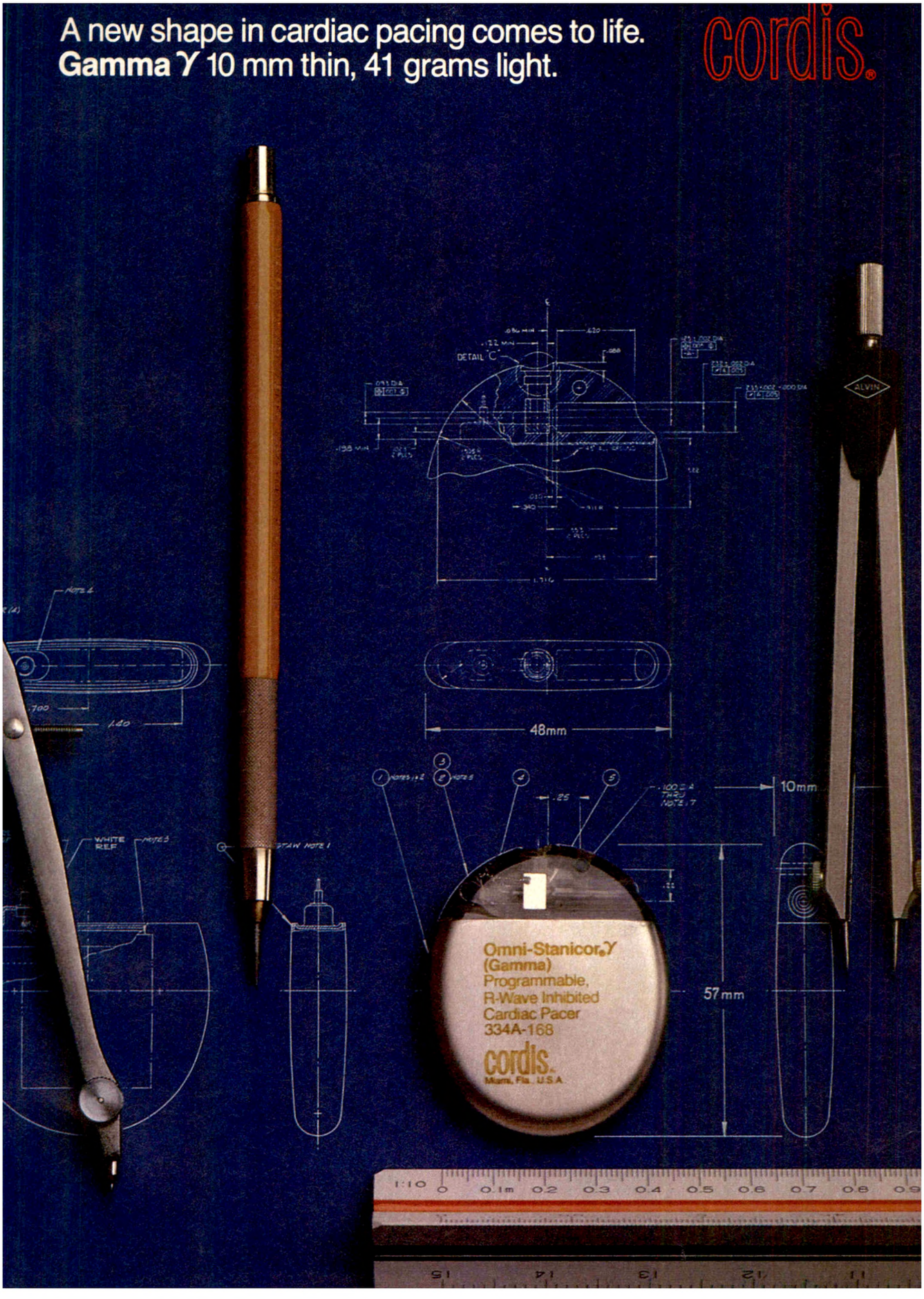
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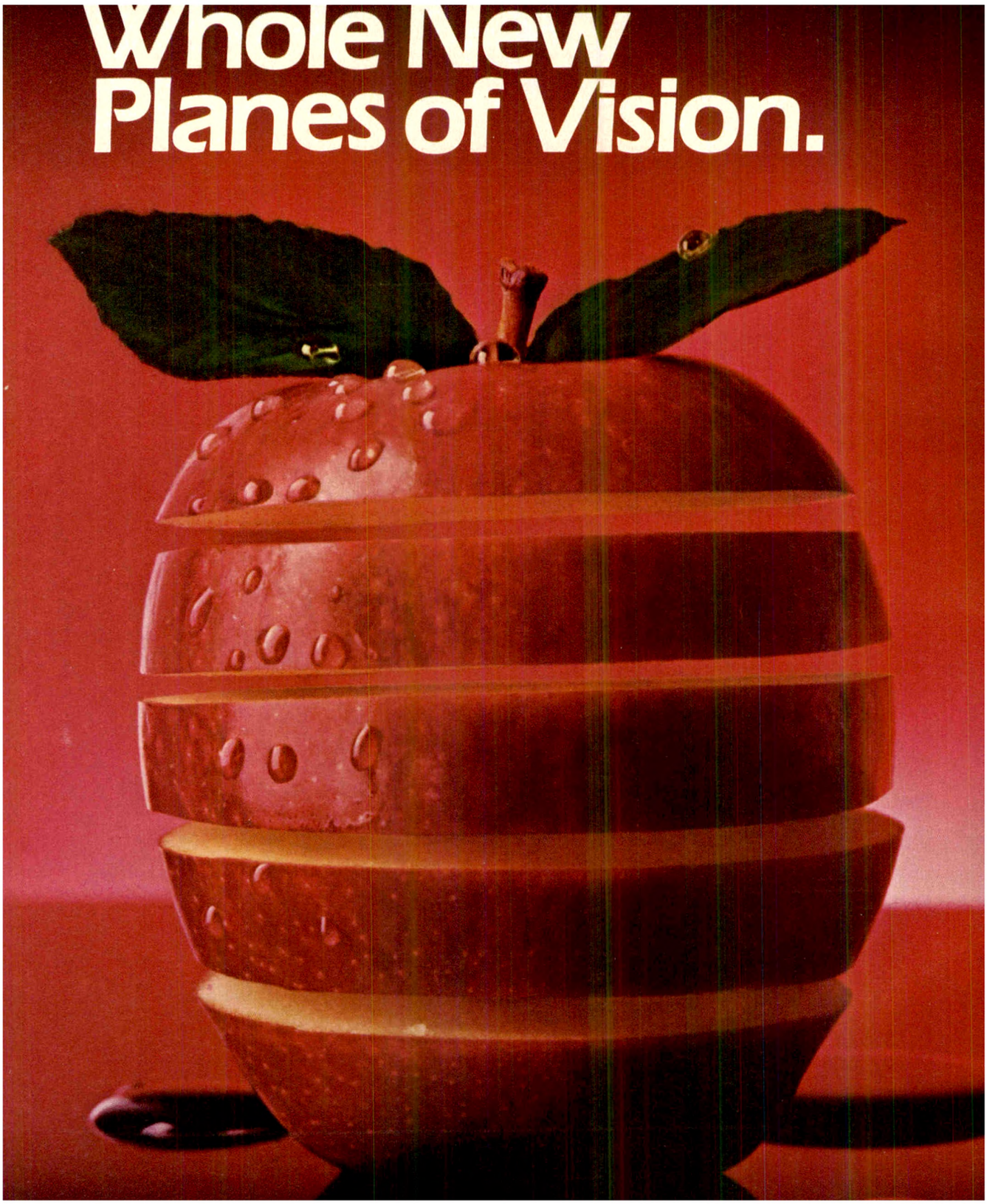
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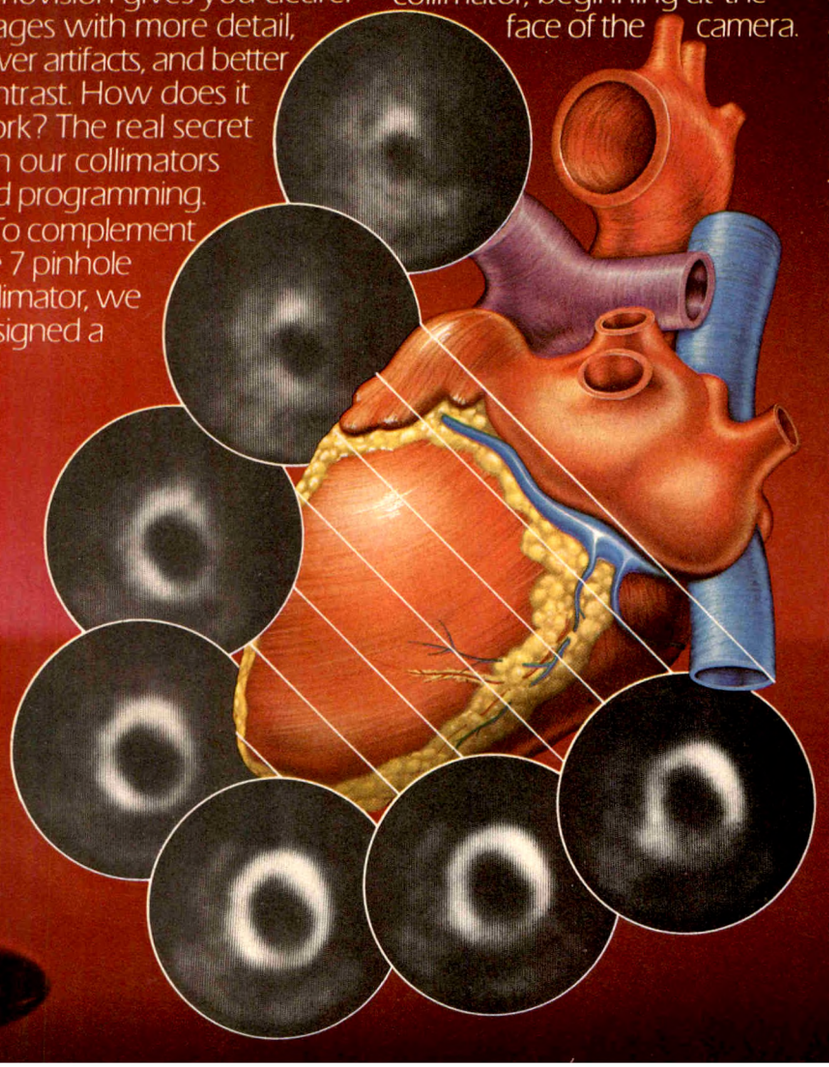

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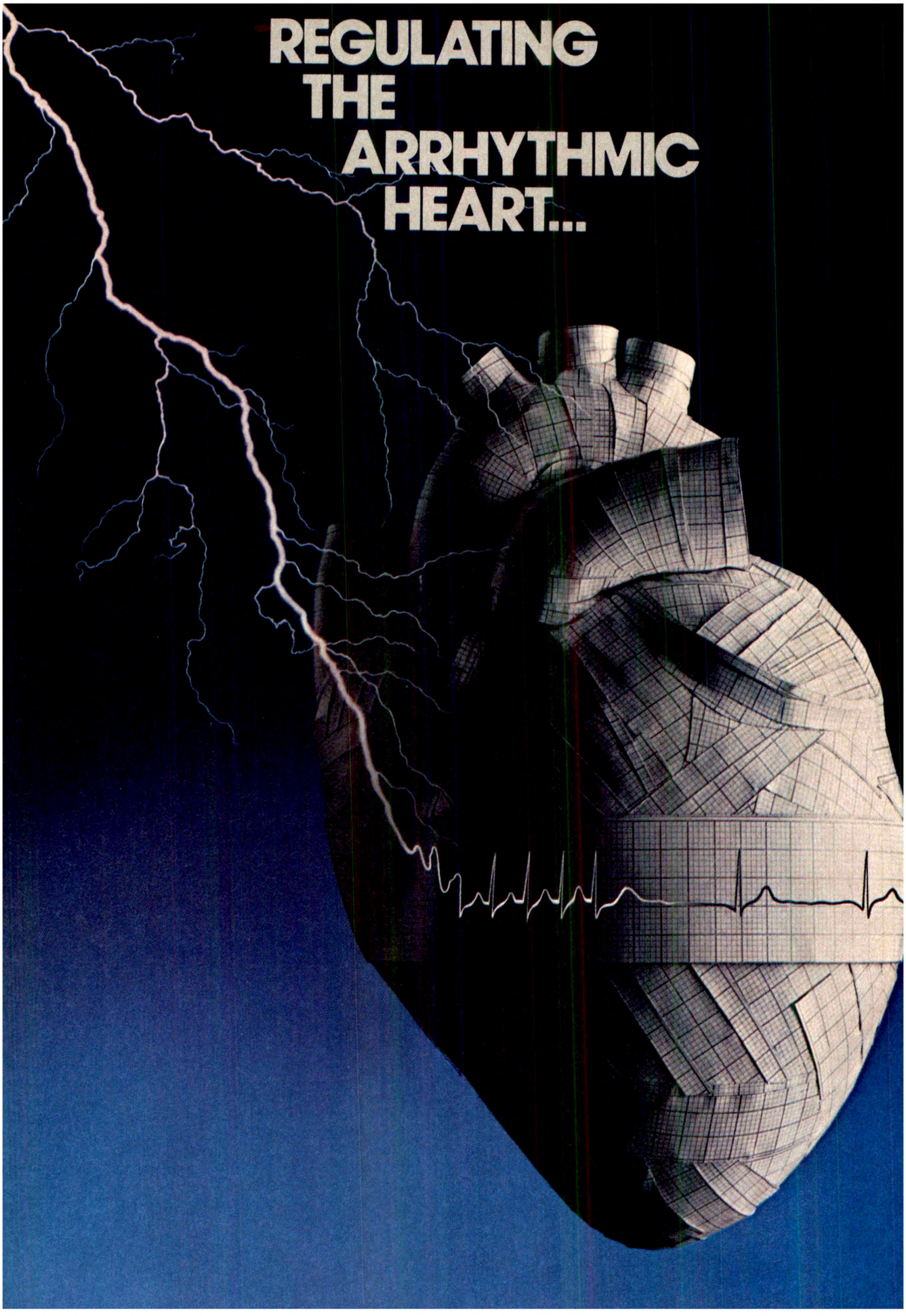
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INSTEAD The arrhythmia is induced by an antiarrhythmic drug such as digitalis or quinidine. Persists after discontinuance of the drug and correction of electrolyte imbalance. Consider INDERAL instead. Often the drug of choice, except in the presence of serious congestive heart failure. Often, too, INDERAL (propranolol HCl) abolishes supraventricular arrhythmias when either digitalis or quinidine has failed.

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*Please turn the page for brief summary of prescribing information on contraindications, adverse reactions, and warnings, including avoidance of abrupt withdrawal.

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Inderal® BRAND OF propranolol hydrochloride **A beta-adrenergic blocking agent**

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias.

Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: Cardiac Arrhythmias: *1.) Supraventricular arrhythmias:* a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias: Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a) Ventricular tachycardias: With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication: If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia. Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation o angina and, in some cases, myocardial infarction, following *abrupt* discontinuation INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dos should be gradually reduced and the patient carefully monitored. In addition, wher INDERAL is prescribed for angina pectoris, the patient should be cautioned agains interruption or cessation of therapy without the physician's advice. If INDERAL ther is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitut INDERAL therapy and take other measures appropriate for the management of uns ble angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term u not been adequately appraised. Special consideration should be given to propranolol's tial for aggravating congestive heart failure. Propranolol may mask the clinical signs of ing or continuing hyperthyroidism or complications and give a false impression of impro Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of sym of hyperthyroidism, including thyroid storm. This is another reason for withdrawing prop slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have be ported in which, after propranolol, the tachycardia was replaced by a severe bradycard quiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg prop

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release f tenance of adequate cardiac function, beta blockade will impair the desired inotropic e Therefore, INDERAL should be titrated carefully when administered for arrhythmias occ during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of t heart to respond to reflex stimuli. For this reason, with the exception of pheochromocyto INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and siologic effects are gone according to available evidence. However, in case of emergen gery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can b versed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, su tients may be subject to protracted severe hypotension. Difficulty in restarting and main the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONC EMPHYSEMA), INDERAL should be administered with caution since it may block broncl tion produced by endogenous and exogenous catecholamine stimulation of beta recep

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adre blocking activity, INDERAL may prevent the appearance of premonitory signs and symp (pulse rate and pressure changes) of acute hypoglycemia. This is especially important t in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by cipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been es tablished. Use of any drug in pregnancy or women of childbearing potential requires tha possible risk to mother and/or fetus be weighed against the expected therapeutic benef bryotoxic effects have been seen in animal studies at doses about 10 times the maximun ommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine s be closely observed if INDERAL is administered. The added catecholamine blocking ac this drug may then produce an excessive reduction of the resting sympathetic nervous a Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be served at regular intervals. The drug should be used with caution in patients with impaire or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensif of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Rayn type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomni tude, weakness, fatigue; reversible mental depression progressing to catatonia; visual d bances; hallucinations; an acute reversible syndrome characterized by disorientation fo and place, short term memory loss, emotional lability, slightly clouded sensorium, and de creased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea stipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with ac and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic pur

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin rous membranes and conjunctivae reported for a beta blocker (practolol) have not been clusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe he ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL is different for ea indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three da to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of ino ble tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE At this time the data on the use of the drug in this age group are t ited to permit adequate directions for use.

INTRAVENOUS Intravenous administration is reserved for life-threatening arrhythmias those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under c monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administratior should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pre and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the action even when a slow circulation is present. If necessary, a second dose may be given two minutes. Thereafter, additional drug should not be given in less than four hours. Addit INDERAL should not be given when the desired alteration in rate and/or rhythm is achiev

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the agement of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE C EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPON VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE DENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

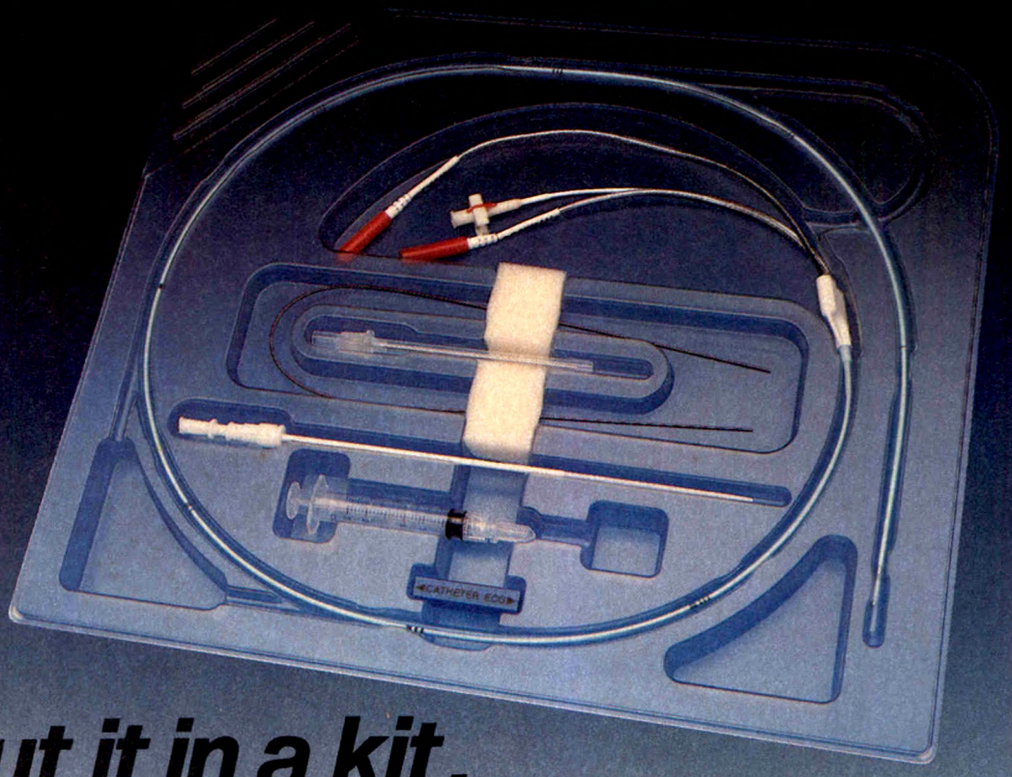
HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS: *No. 461*—Each scored tablet contains 10 mg of propranolol hydrochloride, in b of 100 and 1,000. Also in unit dose package of 100. *No. 462*—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package 100. *No. 464*—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles 100 and 1,000. Also in unit dose package of 100. *No. 468*—Each scored tablet contains 8(of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE: *No. 3265*—Each ml contains 1 mg of propranolol hydrochloride in Water for tion. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

How do you improve on the Swan-Ganz® Pacing Catheter?



Put it in a kit.

The Swan-Ganz Bipolar Pacing Catheter has been shown to provide excellent pacing stability and is well known for its ease of insertion. Now you can get this proven performance with all the convenience of a ready-to-use kit.

A rapid, reliable bedside procedure.

Clinical experience has shown that insertion can be performed at bedside in minutes by using an ECG recording from the distal electrode as a placement guide. Blood flow directs the balloon-tipped catheter rapidly into the right ventricle. No fluoroscopy is needed. Both the catheter body and electrodes are radiopaque and may be visualized by fluoroscopy, if desired.

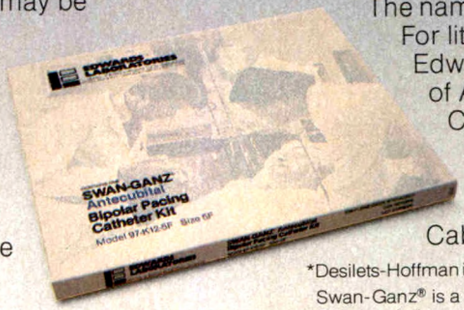
Quality components for quality pacing.

In addition to the 5-F Swan-Ganz Bipolar Pacing Catheter, the kit contains the basic components needed for prompt, reliable catheter placement: a Desilets-Hoffman* type percutaneous insertion set for maximum ease in insertion, a unique syringe designed to ensure proper balloon inflation and a convenient ECG adapter.

Two types of kits are available. One is designed for antecubital, subclavian or internal jugular vein insertion. The other, for femoral insertion, has a "J" shaped tip to facilitate entry from the inferior vena cava. Either may be used with most external pacemakers.

So now get reliable emergency pacing and ease of insertion with all the convenience of a ready-to-use kit.

The Swan-Ganz Bipolar Pacing Catheter Kit. The name to rely on for quality pacing.



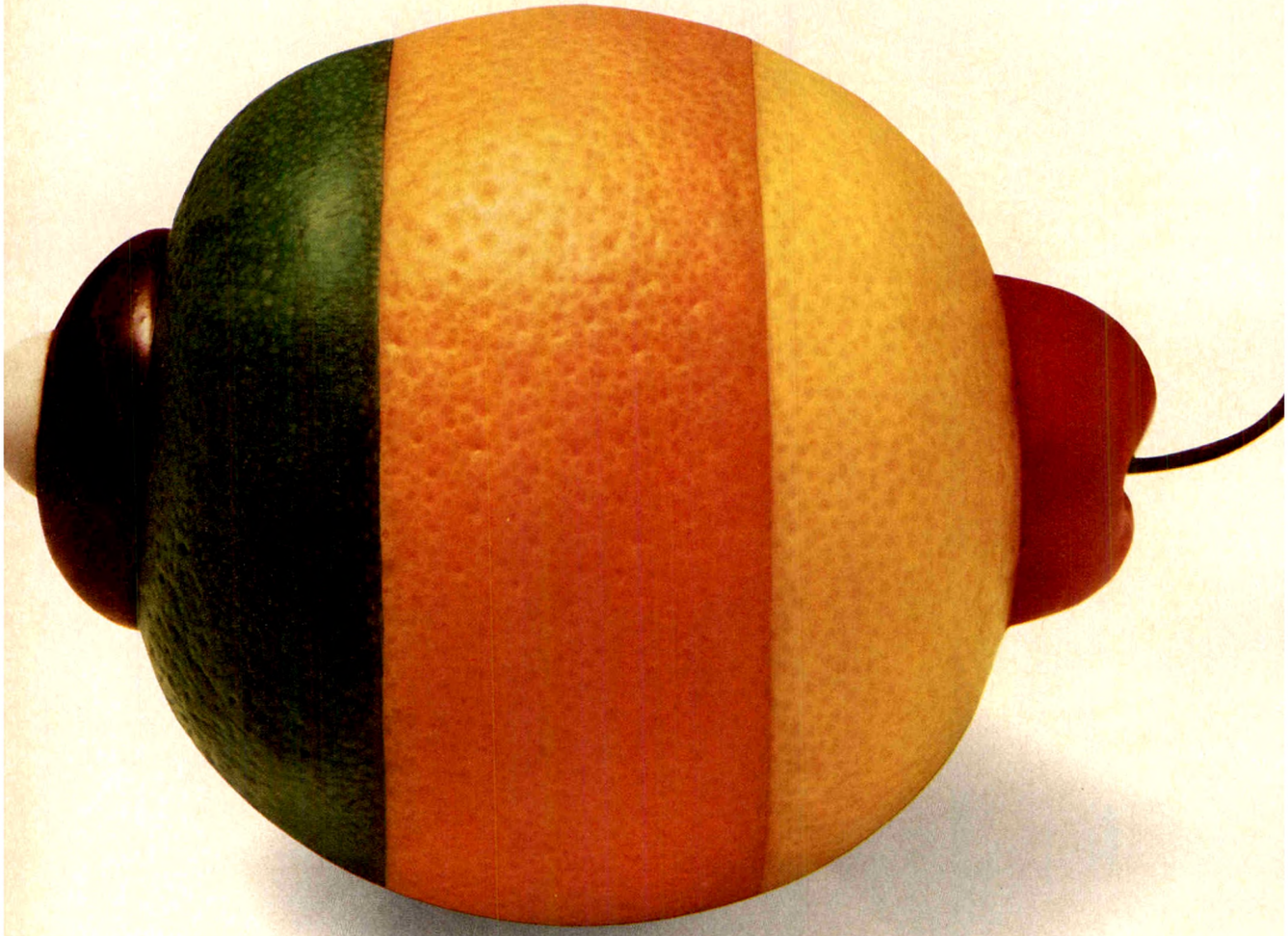
For literature, contact: American Edwards Laboratories, Division of American Hospital Supply Corporation, 17221 Red Hill Avenue, (Irvine), P.O. Box 11150, Santa Ana, CA 92711. Telephone: 714/557-8910, Cable: EDSLAB. Telex: 68-5567.

*Desilets-Hoffman is a registered trademark of C. R. Bard, Inc.

Swan-Ganz® is a registered trademark, American Edwards Laboratories

American Edwards Laboratories

Fruitless?



A Question of Compliance.

Patients on potassium supplements *won't* comply if they tire of the sweet fruity taste used to mask the "bitter pill" of potassium in their medication.

That's when a prescription for the fruitless taste of KATO potassium supplement can be fruitful.

KATO Supplement. The compatible taste of tomato.

In KATO supplement, the naturally tangy taste of tomato *complements* the naturally salty taste of potassium chloride. Patients like the combination, and will stay with it day after day. Tomato-flavored KATO supplement is a natural — at breakfast and dinner.

KATO Supplement. The preferred salt in the preferred form.

Each single-dose packet of KATO supplement contains 20 mEq of potassium chloride — the preferred salt — and less than 5 mg sodium chloride. Because it contains the chloride salt, KATO supplement can be used where hypochloremic alkalosis is also a problem. KATO supplement mixes easily in water or tomato juice, and just two packets daily provide a full therapeutic dose.

Fruitful.



KATO Supplement.
It's fruitless for fruitful compliance.

- tangy, tomato taste well accepted for long-term compliance
- B.I.D. regimen encourages compliance
- liquid form minimizes potential for gastrointestinal irritation
- corrects both hypokalemia and hypochloremic alkalosis
- convenient, easy-to-carry single-dose packets



KATO®
(potassium chloride
for oral solution) 20 mEq
(1.5 g KCl)

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PUERTO RICO 00661

Please see prescribing information on following page.

KATO®
(potassium chloride for oral solution)

20 mEq (1.5 g KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains approximately 0.5 mEq sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6-gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

HOW SUPPLIED:
Cartons of 30 and 120 6-gram unit dose packets, 20 mEq each.

CAUTION:
Federal law prohibits dispensing without a prescription.

02-488-30-1
1-80

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PUERTO RICO 00661

When exact measurement of home exercise programs is essential.....



The Amerec Tunturi Ergometer

With the Amerec Tunturi, physician, therapist and patient all know exactly how much exercise is being performed. Progressive rehabilitation programs can be monitored and adjusted with confidence. The brake scale accurately registers the amount of energy expended in watts—at both 50 and 60 revolutions per minute. Tension adjustment is infinitely variable. Disc brakes apply quiet, even resistance. And the easy-to-read tachometer/odometer registers revolutions per minute and total distance pedalled.

The Amerec Tunturi is as convenient as it is accurate. The flywheel acts as a caster to roll where needed. An effective exercise program requires less than a square yard of floor space.

Learn about the other features of this advanced, Finnish-built ergometer. We'll forward complete details at your request. Write Amerec, Box 3825, Bellevue, Washington 98009. (800) 426-0858.

AMEREC

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DVERTISEMENT

Antiarrhythmia Bulletin No. 2

Quinidine Withdrawal or Replacement May Decrease Physiologic Effect of Digoxin

Some Further Reports on Problems Arising From the Quinidine-Digoxin Interaction

"An increase in serum digoxin concentration after quinidine is added is now anticipated by many physicians. The opposite is predictable from this observation: a fall in the serum concentration and physiologic effect of digoxin when quinidine is withdrawn from a patient previously stable on both drugs. Although an example of this fall has been reported, little emphasis has been given to this aspect of the quinidine-digoxin interaction, which may have important consequences....

"It appears that this [a 62-year-old female] patient's symptoms and increase in ventricular rate were due to a decrease in serum digoxin concentration and physiologic effect caused by withdrawal of quinidine. This phenomenon should be anticipated when quinidine is discontinued or replaced by other antiarrhythmic therapy in patients previously stable on digoxin and quinidine, especially those in atrial fibrillation, and may require an appropriate readjustment of digoxin dosage based on clinical observations and measured serum digoxin concentrations."

—From Moench, T.R.: The Quinidine-Digoxin Interaction, N. Engl. J. Med. *302*:864, 1980.

"Dr. Moench reports a case that supports the view that quinidine withdrawal can decrease the effect of digoxin. The end point in his study was the time-honored ventricular response to atrial fibrillation, i.e., atrioventricular nodal conduction. His case report provides another bit of evidence that the change in serum digoxin concentration during the interaction often reflects the effect of digoxin on the heart. This hypothesis is difficult to test, and the observations of Dr. Moench are helpful in view of the increasingly complex picture of the interaction."

—From Bigger, J.T., Jr.: The Quinidine-Digoxin Interaction, N. Engl. J. Med. *302*:864–865, 1980.

Do Other Antiarrhythmics Interact With Digoxin?

"We compared the effects of quinidine and three alternate antiarrhythmic drugs on serum digoxin concentration in 63 patients before and during administration of quinidine, procainamide, disopyramide, or mexiletine. Quinidine increased digoxin concentration by at least 0.5 nmol/L in 21 of 22 patients: Mean serum digoxin rose from 1.2 nmol/L to 2.4 nmol/L ($P<0.001$). Procainamide, disopyramide, or mexiletine increased serum digoxin by 0.5 nmol/L in one of 41 patients. Anorexia, nausea, and vomiting developed soon after starting quinidine therapy in 10 of the 22 patients who received quinidine but in only five of the 41 patients who received procainamide, disopyramide, or mexiletine ($P<0.01$). Quinidine prolonged the PR interval from 160 ± 14 ms to 183 ± 26 ms, but procainamide, disopyramide, and mexiletine did not change the PR interval ($P < 0.005$). In digitalized patients, quinidine increases serum digoxin concentration, increases digoxin's effect on atrioventricular conduction, and produces more adverse gastrointestinal effects than procainamide, disopyramide, or mexiletine....

"Figure 1 shows the change in serum digoxin concentrations during administration of the four antiarrhythmic drugs. Each dot represents, for one patient, the difference between the mean serum digoxin concentration before and during therapy with quinidine, procainamide, disopyramide, or mexiletine....

"Because interaction between digoxin and quinidine is common and because quinidine's potential for producing toxicity is still unknown, we recommend that caution be exercised when quinidine is given to digitalized patients....

"Our study shows that several other orally active antiarrhythmic drugs fail to cause an increase in serum digoxin concentration."

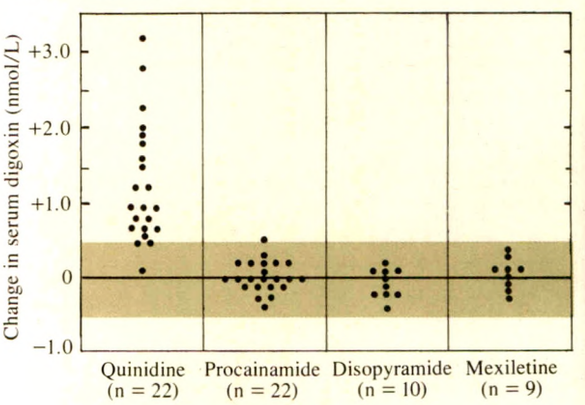


Figure 1.

—From Leahey, E.B., Jr., and others: The Effect of Quinidine and Other Oral Antiarrhythmic Drugs on Serum Digoxin: A Prospective Study, Ann. Intern. Med. *92*:605–608, 1980.

From what has appeared in the literature concerning the elevation of digoxin levels with concomitant quinidine use and reported lack of elevation of digoxin levels with concomitant Norpace® (disopyramide phosphate) use, it would appear that Norpace could be a logical alternative to quinidine in some patients using digoxin concomitantly.

Please see the next page for complete prescribing information

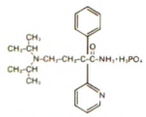
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NORPACE® CAPSULES (disopyramide phosphate)

DESCRIPTION

Norpace (disopyramide phosphate) is an antiarrhythmic drug available for oral administration in capsules containing 100 mg or 150 mg of disopyramide base, present as the phosphate. The base content of the phosphate salt is 77.6%.

The structural formula of Norpace is seen at the right. Norpace is freely soluble in water, and the free base (pKa 8.36) has an aqueous solubility of 1 mg/ml. The chloroform: water partition coefficient of the base is 3.1 at pH 7.2. Norpace is a racemic mixture of *d*- and *l*-isomers. This drug is not chemically related to other antiarrhythmic drugs.



α-[2-(diisopropylamino) ethyl]-α-phenyl-2-pyridineacetamide phosphate

CLINICAL PHARMACOLOGY

Mechanisms of action: Norpace (disopyramide phosphate) is a Type 1 antiarrhythmic drug (i.e., similar to procainamide and quinidine). *In animal studies* Norpace decreases the rate of diastolic depolarization (phase 4) in cells with augmented automaticity, decreases the upstroke velocity (phase 0) and increases the action potential duration of normal cardiac cells, decreases the disparity in refractoriness between infarcted and adjacent normally perfused myocardium and has no effect on alpha- or beta-adrenergic receptors.

Electrophysiology: In man, Norpace at therapeutic plasma levels shortens the sinus node recovery time, lengthens the effective refractory period of the atrium and has a minimal effect on the effective refractory period of the AV node. Little effect has been shown on AV-nodal and His-Purkinje conduction times or QRS duration. However, prolongation of conduction in accessory pathways occurs.

Hemodynamics: At recommended oral doses, Norpace rarely produces significant alterations of blood pressure in patients without congestive heart failure (see *Warnings*). Intravenous injection (2 mg/kg over 3 minutes) produces a moderate, transient increase in heart rate and in total peripheral resistance. In patients with organic heart disease intravenous Norpace causes cardiac depression, with approximately a 10% reduction of cardiac output.

Anticholinergic activity: The *in vitro* anticholinergic activity of Norpace is approximately 0.06% that of atropine; however, the usual dose of Norpace is 150 mg every 6 hours compared to 0.4-0.6 mg for atropine (see *Warnings* and *Adverse Reactions* for anticholinergic side effects).

Pharmacokinetics: Following oral administration disopyramide phosphate is rapidly and almost completely absorbed, and peak plasma levels are usually attained within two hours. The usual therapeutic plasma levels of disopyramide *free base* are 2-4 mcg/ml and at these concentrations protein binding varies from 50-65%. Because of concentration-dependent protein binding, it is difficult to predict the concentration of the free drug when total drug is measured.

The mean plasma half-life of disopyramide in healthy humans is 6.7 hours (range of 4 to 10 hours). In six patients with impaired renal function (creatinine clearance less than 40 ml/min), disopyramide half-life values were 8 to 18 hours.

In healthy men about 50% of a given dose of disopyramide is excreted in the urine as the unchanged drug, about 20% as the mono-N-dealkylated metabolite and 10% as the other metabolites. The plasma concentration of the major metabolite is approximately one tenth that of disopyramide. Altering the urinary pH in man does not affect the plasma half-life of disopyramide.

INDICATIONS

Norpace should be prescribed only after appropriate electrocardiographic assessment.

Norpace (disopyramide phosphate) is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination:

1. Unifocal premature (ectopic) ventricular contractions.
2. Premature (ectopic) ventricular contractions of multifocal origin.
3. Paired premature ventricular contractions (couplets).
4. Episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

In controlled trials of ambulatory patients Norpace was as effective as 325 mg quinidine q 6 h in reducing the frequency of ventricular ectopic activity. Norpace was equally effective in digitalized and nondigitalized patients. Norpace is also equally effective in the treatment of primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease.

Oral Norpace (disopyramide phosphate) has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias.

Type 1 antiarrhythmic drugs are usually not effective in treating arrhythmias secondary to digitalis intoxication and, therefore, Norpace is not indicated for such cases.

The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

CONTRAINDICATIONS

Norpace (disopyramide phosphate) is contraindicated in the presence of cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

WARNINGS

Negative inotropic properties: Heart failure/hypotension: **Norpace may cause or worsen congestive heart failure or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. Norpace should not be used in patients with uncompensated or marginally compensated congestive heart failure or hypotension unless the congestive heart failure or hypotension is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace, but careful attention must be given to the maintenance of cardiac function, including optimal digitalization. If hypotension occurs or congestive heart failure worsens, Norpace should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established.**

QRS widening: **Although it is unusual, significant widening (greater than 25%) of the QRS complex may occur during Norpace administration; in such cases Norpace (disopyramide phosphate) should be discontinued.**

Q-T prolongation: **As with other Type 1 antiarrhythmic drugs, prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If a Q-T prolongation of greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and consideration be given to discontinuing Norpace (disopyramide phosphate).**

Hypoglycemia: **In rare instances significant lowering of blood glucose values has been reported during Norpace administration.** The physician should be alert to this possibility, especially in patients with congestive heart failure, chronic malnutrition, hepatic, renal or other diseases or drugs (e.g., beta adrenoceptor blockers, alcohol) which could compromise preservation of the normal glucoregulatory mechanisms in the absence of food. In these patients the blood glucose levels should be carefully followed.

Concomitant antiarrhythmic therapy: **The concomitant use of Norpace with other Type 1 antiarrhythmic agents (such as quinidine or procainamide) and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction.** This should be considered particularly in patients with any degree of cardiac decompensation or those with a prior history thereof. Patients receiving more than one antiarrhythmic drug must be carefully monitored.

Heart block: **If first-degree heart block develops in a patient receiving Norpace, the dosage should be reduced.** If the block persists despite reduction of dosage, continuation of the drug must depend upon weighing the benefit being obtained against the risk of higher degrees of heart block. Development of second- or third-degree AV block or unifascicular, bifascicular or trifascicular block requires discontinuation of Norpace therapy, unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker.

Anticholinergic activity: **Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention unless adequate overriding measures are taken;** these consist of the topical application of potent miotics (e.g., pilocarpine) for patients with glaucoma, and catheter drainage or operative relief for patients with urinary retention. Urinary retention may occur in patients of either sex as a consequence of Norpace administration, but males with benign prostatic hypertrophy are at particular risk. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace therapy. Norpace should be used with special care in patients with myasthenia gravis since its anticholinergic properties could precipitate a myasthenic crisis in such patients.

PRECAUTIONS

Atrial tachyarrhythmias: Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not result in an increase of ventricular rate beyond physiologically acceptable limits.

Conduction abnormalities: Care should be taken when prescribing Norpace for patients with sick sinus syndrome (bradycardia-tachycardia syndrome), Wolff-Parkinson-White syndrome (WPW), or bundle branch block. The effect of Norpace (disopyramide phosphate) in these conditions is uncertain at present.

Cardiomyopathy: Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace, probably due to cardiodepressant mechanisms. Therefore, a loading dose of Norpace should not be given to such patients and initial dosage and subsequent dosage adjustments should be made under close supervision (see *Dosage and Administration*).

Drug interactions: Other antiarrhythmic drugs (e.g., quinidine, procainamide, lidocaine, propranolol) have occasionally been used concurrently with Norpace but no specific drug interaction studies have been conducted (see *Warnings*). Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in these situations. Norpace does not increase serum digoxin levels.

Renal impairment: More than 50% of disopyramide is excreted in the urine unchanged. Therefore Norpace dosage should be reduced in patients with impaired renal function (see *Dosage and Administration*). The electrocardiogram should be carefully monitored for prolongation of PR interval, evidence of QRS widening or other signs of overdosage (see *Overdosage*).

Hepatic impairment: Hepatic impairment also causes an increase in the plasma half-life of disopyramide. Dosage should be reduced for patients with such impairment. The electrocardiogram should be carefully monitored for signs of overdosage (see *Overdosage*).

Hypokalemia: Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace (disopyramide phosphate) therapy.

Pregnancy: Reproduction studies in rats and teratology studies performed both in rats and in rabbits have revealed minimal evidence of impaired fertility. No fetal anomalies were attributable to Norpace. Disopyramide has been found in human fetal blood. However, well-controlled studies of Norpace have not been performed in pregnant women and experience with Norpace during pregnancy is limited; therefore the possibility of damage to the fetus cannot be excluded.

Norpace has been reported to stimulate contractions of the pregnant uterus. Norpace (disopyramide phosphate) should be used in pregnant women only when it is clearly indicated and the benefit/risk ratio has been carefully evaluated.

Labor and delivery: It is not known whether the use of Norpace during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention.

Nursing mothers: Studies in rats have shown that the concentration of disopyramide and its metabolite is between one and three times greater in milk than it is in plasma. Following oral administration, disopyramide has been detected in human milk at a concentration not exceeding that in plasma. Therefore, if use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

ADVERSE REACTIONS

The adverse reactions which were reported in clinical trials encompass observations in 1,500 patients, including 90 patients studied for at least four years. The most serious adverse reactions are hypotension and congestive heart failure. The most common adverse reactions, which are dose dependent, are associated with the anticholinergic properties of the drug. These may be transitory, but may be persistent or can be severe. Urinary retention is the most serious anticholinergic effect.

The following reactions were reported in 10-40% of patients:

Anticholinergic: dry mouth (32%), urinary hesitancy (14%), constipation (11%)

The following reactions were reported in 3-9% of patients:

Anticholinergic: blurred vision, dry nose/eyes/throat
Genitourinary: urinary frequency and urgency
Gastrointestinal: nausea, pain/bloating/gas
General: dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains

The following reactions were reported in 1-3% of patients:

Anticholinergic: urinary retention
Genitourinary: impotence
Cardiovascular: hypotension with or without congestive heart failure, increased congestive heart failure (see *Warnings*), cardiac conduction disturbances (see *Warnings*), edema/weight gain, shortness of breath, syncope, chest pain
Gastrointestinal: anorexia, diarrhea, vomiting
Dermatologic: generalized rash/dermatoses, itching
Central nervous system: nervousness
Other: hypokalemia, elevated cholesterol/triglycerides

The following reactions were reported in less than 1%:

Depression, insomnia, dysuria, numbness/tingling, elevated liver enzymes, AV block, elevated BUN, elevated creatinine, decreased hemoglobin/hematocrit

Hypoglycemia has been reported in association with Norpace (disopyramide phosphate) administration (see *Warnings*).

Rarely, acute psychosis has been reported following Norpace therapy, with prompt return to normal mental status when therapy was stopped. Infrequent occurrences of reversible cholestatic jaundice have been reported in association with disopyramide therapy as have rare instances of reversible agranulocytosis. The physician should be aware of these possible reactions and should discontinue Norpace therapy promptly if they occur.

DOSAGE AND ADMINISTRATION

The dosage of Norpace (disopyramide phosphate) must be individualized for each patient on the basis of response and tolerance. The usual adult dosage of Norpace is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients whose body weight is less than 110 pounds (50 kg), the recommended dosage is 100 mg every six hours.

For patients with cardiomyopathy or possible cardiac decompensation, a loading dose, as discussed below, should not be given and initial dosage should be limited to 100 mg of Norpace every six hours. Subsequent dosage adjustments should be made gradually, with close monitoring for the possible development of hypotension and/or congestive heart failure (see *Warnings*).

For patients with moderate renal insufficiency (creatinine clearance greater than 40 ml/min) or hepatic insufficiency, Norpace dosage of 100 mg every six hours is recommended, with or without an initial loading dose of 200 mg.

For patients with severe renal insufficiency (C_{Cr} less than 40 ml/min) the recommended dosage regimen is an initial loading dose of 150 mg followed by a maintenance dose of 100 mg at intervals shown in the table below:

NORPACE DOSAGE INTERVAL FOR PATIENTS WITH RENAL INSUFFICIENCY

Creatinine clearance (ml/min)	40-30	30-15	less than 15
Approximate maintenance-dosing interval	q 8 hr	q 12 hr	q 24 hr

For patients in whom rapid control of ventricular arrhythmia is essential, an initial loading dose of 300 mg Norpace (200 mg for patients whose body weight is less than 110 pounds) is recommended, followed by appropriate maintenance dosage. Therapeutic effects are usually attained 30 minutes to three hours after administration of a 300-mg loading dose. If there is no response nor evidence of toxicity within six hours the loading dose, 200 mg every six hours may be prescribed instead of the usual 150 mg. If there is no response to this dosage within 48 hours, either Norpace should then be discontinued or the physician should consider hospitalizing the patient for careful monitoring while subsequent doses of 250 or 300 mg every six hours are given. A limited number of patients with severe refractory ventricular tachycardia have tolerated daily doses of Norpace up to 1600 mg per day (400 mg every 6 hours) resulting in disopyramide plasma levels up to 9 mcg/ml. If such treatment is warranted, it is essential that patients be hospitalized for close evaluation and continuous monitoring.

Transferring to Norpace: The following dosage schedule based on theoretical considerations rather than experimental data is suggested for transferring patients with normal renal function from either quinidine sulfate or procainamide therapy (Type 1 antiarrhythmic agents) to Norpace therapy.

Norpace may be started using the regular maintenance schedule **without a loading dose** 6-12 hours after the last dose of quinidine sulfate or 3-6 hours after the last dose of procainamide.

In patients where withdrawal of quinidine sulfate or procainamide is likely to produce life-threatening arrhythmias, the physician should consider hospitalization of the patient.

OVERDOSAGE

No specific antidote for Norpace has been identified. Treatment of overdosage should be supportive and may include the administration of isoproterenol, dopamine, hemoperfusion with charcoal, hemodialysis, intra-aortic balloon counterpulsation and mechanically assisted respiration.

In vitro studies with human blood have demonstrated good dialyzability for disopyramide. Its clearance was 33 ml/min at a blood flow of 250 ml/min when an initial plasma concentration of 22 mcg/ml was dialyzed using an artificial kidney (Cordis-DOW-4).

On the basis of animal studies toxic plasma levels of disopyramide might be expected to produce excessive widening of the QRS complex and Q-T interval, worsening of congestive heart failure, hypotension, various kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required.

HOW SUPPLIED

Norpace (disopyramide phosphate) is supplied in hard gelatin capsules containing either 100 mg or 150 mg of disopyramide base.

Norpace 100-mg capsules are white and orange, with markings SEARLE and 2752. Norpace 150-mg capsules are brown and orange, with markings SEARLE and 2762.

Available in bottles of 100, 500, and 1,000 capsules, and cartons of 100 unit-dose individually blister-sealed capsules.

SEARLE *Searle Laboratories*
Division of Searle Pharmaceuticals Inc.
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Continuous Fractionated Electrical Activity After Stimulation of the Ventricles During the Vulnerable Period: Evidence for Local Reentry

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Ventricular multiple extrasystoles and fibrillation were induced in open chest dogs by the delivery of either a single electrical pulse or a train of pulses to the right ventricle during the vulnerable period of the cardiac cycle. Bipolar epicardial electrodes delivered current while bipolar plunge electrodes recorded the activation complexes at various distances from the stimulation site. At stimulus intensities below the threshold for multiple ventricular responses, the electrograms recorded from muscle adjacent to the stimulation site showed fragmented activation complexes that lasted considerably longer than the control complexes. At stimulus intensities that evoked multiple ventricular extrasystoles or fibrillation, the fragmented electrical activity became continuous and bridged the diastolic interval between successive ectopic complexes. The continuous fractionated electrical activity that preceded the appearance of multiple extrasystoles and fibrillation was recorded only from electrodes placed within a few millimeters of the stimulating electrodes and could be evoked only by stimulation during the vulnerable period. Disappearance of the fractionated local electrical activity during a run of extrasystoles was followed immediately by the resumption of a normal rhythm. In addition, the fractionated continuous electrical activity that appeared after delivery of a single stimulus during the vulnerable period could be abolished by the delivery of a second stimulus during the protective zone. The presence of continuous local electrical activity before the development of multiple extrasystoles and fibrillation provides strong evidence that the ventricular fibrillation threshold technique operates by producing local reentrant activity.

The experiments of Wiggers and Wegria[1] in 1940 first demonstrated that an appropriately timed electrical stimulus of sufficient energy delivered to the ventricles in late systole could result in ventricular fibrillation. These investigators[2] later defined the "ventricular fibrillation threshold" as the current strength of a brief direct current shock of constant duration (0.01–0.03 s) that is just able to induce fibrillation when applied during the vulnerable period of late systole. To minimize the amount of time required to locate the vulnerable period precisely, Han[3] introduced a technique for measuring vulnerability to fibrillation in which a train of constant current pulses scanned the T wave of the electrocardiogram. Although many studies have used electrical stimulation of the ventricles to assess vulnerability to fibrillation, the mechanism by which current delivered during the vulnerable period initiates fibrillation remains unknown. Moe et al.[4] demonstrated that ventricular fibrillation induced by a single stimulus delivered during the vulnerable period began with a series of multiple extrasystoles originating from the vicinity of the stimulating electrodes. By mapping the spread of activation of the initial extrasystoles with bipolar electrograms they eliminated the possibility of a macroreentrant circuit and suggested that the initial

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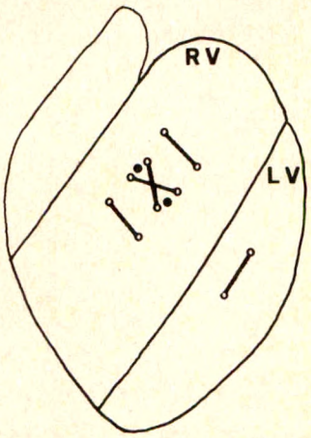


FIGURE 1. Schematic diagram of the heart indicating the placement of stimulating and recording electrodes. **Solid circles** indicate the position of the bipolar electrodes used to deliver current during the vulnerable period (interelectrode distance 7 mm). **Open circles** indicate the position of the bipolar recording electrodes on the right (RV) and left (LV) ventricles. The two recording electrodes in each pair were separated by a distance of 5 to 7 mm.

impulses originated from an automatic center created by the stimulus current. However, because the direct bipolar recordings made by Moe et al.[4] were never closer than 6 mm from the stimulating electrodes, they were unable to eliminate the possibility of local reentry.

Recent studies in both human subjects[5] and experimental animals[6,7] have suggested that local reentry can be identified in bipolar electrograms as the presence of continuous electrical activity bridging the diastolic interval between consecutive ectopic complexes. Thus, the purpose of the present experiments was to use multiple bipolar electrograms to locate areas of continuous electrical activity that precede the development of multiple extrasystoles and fibrillation when current is applied to the myocardium during the vulnerable period.

Methods

Experimental preparation: Experiments were performe in 12 adult mongrel dogs weighing 13 to 20 kg. The dogs wer anesthetized with sodium pentobarbital (30 mg/kg bod weight intravenously) and ventilated with room air with us of a positive pressure respirator (Harvard 607). A left thora cotomy was performed in the fourth and fifth intercosta spaces and the fifth rib removed. The stellate ganglia wer decentralized bilaterally to slow the spontaneous heart rat and intramural bipolar electrodes were applied to the lef atrium to pace the heart at a constant basic cycle length of 40 to 500 ms. A small thermistor probe (YSI 427) was sutured t the left ventricular epicardium and temperature was main tained constant at 37 to 38° C with use of a heating lamp. femoral artery was cannulated and arterial blood pressur monitored continuously throughout the experiment.

Electrophysiologic protocol: Ventricular arrhythmia were induced by passing either a single square wave impuls (10 ms) or a gated train of impulses (14 pulses, 4 ms, 100 hertz through bipolar electrodes during the vulnerable period of th T wave of the electrocardiogram. The stimulating electrode consisted of two 21 gauge stainless steel hypodermic needle embedded in an acrylic plaque. The two needles were sepa rated by 7 mm and extended 2 mm from the surface of th plaque. The trains or single stimuli were synchronized to th atrial stimulus and were delivered after every 15th ventricula response. The single stimuli were delivered to the myocardium beginning in the absolute refractory period and were move by 5 ms increments through the relative refractory period t permit location of the most vulnerable portion of the cardia cycle. In addition to delivery of single pulses during the vul nerable period, in several experiments an additional stimulu was introduced 30 to 50 ms after the initial stimulus in orde to engage the protective zone. When trains of stimuli were delivered during the vulnerable period they were timed t start during the S-T segment of the electrocardiogram and t terminate 20 ms beyond the T wave. The current intensity o all stimuli was measured directly by recording the voltag reduction across a precision 100 ohm resistor in series with th electrodes. When fibrillation occurred in response to either a train of stimuli or a single stimulus, defibrillation wa achieved within 15 seconds with direct current counter shock.

The recording electrodes consisted of Teflon®-coated stainless steel wires (diameter 0.007 inch [0.178 cm]) threaded

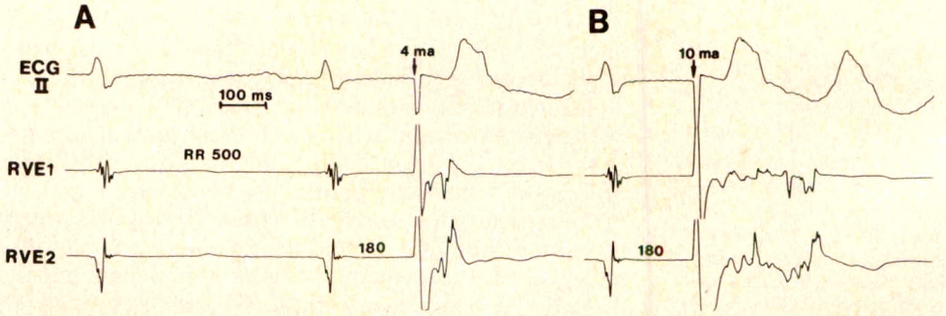


FIGURE 2. The effect of stimulus intensity on the appearance of fractionated electrical activity. Two bipolar electrograms from the right ventricle (RVE1 and RVE2) are shown with a lead II electrocardiogram (ECG). The bipolar electrograms were recorded from electrodes contiguous to the stimulating electrodes (Fig. 1). The atria were driven at a basic cycle length of 500 ms. **A,** after a control cycle, a 4 mA stimulus is delivered to the right ventricle 180 ms after the intrinsic deflection of the basic response in RVE2. A single premature systole appears in the electrocardiogram; both bipolar electrograms show fractionated electrical activity lasting 110 ms beyond the onset of the stimulus artifact. **B,** the stimulus strength is increased to 10 mA, resulting in two premature ventricular complexes. Both bipolar electrograms show fractionated electrical activity that spans the interval in the electrocardiogram between the two premature complexes.

through a 25 gauge hypodermic needle and bent at the tip to form a small hook. The needles were inserted into the myocardium and then withdrawn, leaving the wires hooked into the epicardium.

The positions of the recording electrodes relative to the stimulating electrodes are shown in Figure 1. The two wires in each recording pair were separated by a distance of about 5 to 7 mm. Each pair of recording electrodes was connected to a differential alternating current amplifier (40 to 500 hertz). The bipolar electrograms and a lead II electrocardiogram were displayed on either a Gould-Brush (model 2800) or a Siemens-Elema (Mingograph 804) direct writing recorder at paper speeds of 100 to 250 mm/s.

Results

Response to a single stimulus to right ventricle: The application of high intensity currents to the ventricles during the vulnerable period of the cardiac cycle resulted in the appearance of abnormal extracellular electrical activity. Figure 2 illustrates a typical experiment in which abnormal local electrical activity was observed after the delivery of a single stimulus (10 ms) to the right ventricle during the vulnerable period of the cardiac cycle. The records show the surface electrocardiogram (lead II) and two bipolar right ventricular

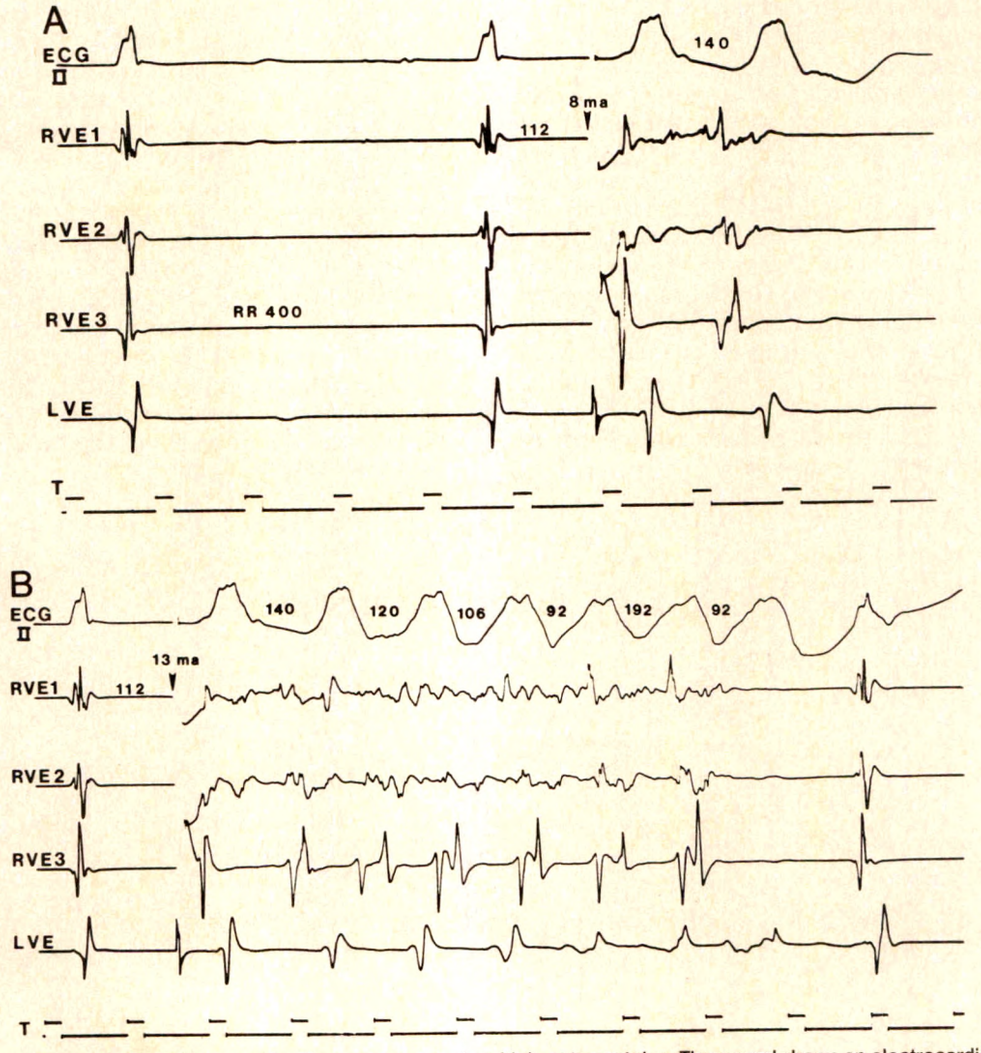


FIGURE 3. Continuous electrical activity preceding the appearance of multiple extrasystoles. The record shows an electrocardiogram (lead II) and four local electrograms (RVE1, RVE2, RVE3 and LVE). RVE1 and RVE2 were recorded from electrodes placed within 2 mm of the stimulating electrodes; RVE3 was recorded 5 mm away from the stimulating electrodes. LVE was obtained from the anterior left ventricle. The time lines (T) at the bottom of each panel indicate 100 ms intervals. **A,** after a control cycle, an 8 mA stimulus (**arrow**) is delivered to the right ventricle at a coupling interval of 112 ms, resulting in two ventricular extrasystoles (R-R interval 140 ms). **B,** the stimulus intensity is increased to 13 mA, resulting in a brief episode of ventricular tachycardia. The tachycardia accelerates during the first four cycles and oscillates in the fifth and sixth cycles before a normal rhythm is restored. In both panels the recording electrodes contiguous to the stimulating electrodes (RVE1 and RVE2) show continuous fractionated activity preceding the onset of each spontaneous ectopic complex. In contrast, RVE3 and LVE display isoelectric lines between successive ectopic complexes. However, the duration of the local activation complexes in these electrograms increases with progressive acceleration of the ectopic complexes.

electrograms (RVE1 and RVE2) recorded from electrodes contiguous to the stimulating electrodes (Fig. 1). Heart rate was held constant at a cycle length of 500 ms. In panel A, a 4 mA stimulus is delivered 180 ms after the intrinsic deflection in RVE2. A stimulus artifact can be seen in all three tracings; the largest is shown in the local bipolar electrograms. After occurrence of the stimulus artifact, a single premature ventricular complex is evident in the surface electrocardiogram, whereas both local electrograms show fractionated electrical activity lasting 110 ms beyond the onset of the stimulus. In panel B, an increase in the current intensity of the stimulus to 10 mA results in the production of two closely coupled extrasystoles in the surface electrocardiogram. Both of the local electrograms display fractionated electrical complexes that span the interval from the stimulus to the onset of the R wave of the second extrasystole in the electrocardiogram.

Figure 3 presents records from another experiment in which abnormal, local electrical activity resulted from ventricular stimulation during the vulnerable period of the cardiac cycle. The records show the surface electrocardiogram (lead II) and two bipolar electrograms (RVE1 and RVE2) recorded from electrodes placed on the right ventricle within 2 mm of the stimulating electrodes. Also shown are an electrogram recorded 5 mm below the stimulation site (RVE3) and one recorded from the anterior surface of the left ventricle (LVE). After the control cycle (Fig. 3A), an 8 mA stimulus is delivered to the right ventricle at a coupling interval of 112 ms. This stimulus results in two ventricular extrasystoles with an R-R coupling interval of 140 ms. The two electrograms recorded very close to the stimulating electrodes (RVE1 and RVE2) display continuous fractionated electrical activity that spans the interval between the two extrasystoles. In contrast to the marked fractionation at the stimulation site, the remote electrograms (RVE3 and LVE) show an isoelectric interval between two discrete activation complexes. The second complex in RVE3 is considerably longer than the first, indicating a more asynchronous spread of activity away from the stimulation site. In Figure 3B, the stimulus intensity is increased to 13 mA, resulting in a run of six spontaneous extrasystoles after the initial stimulus-induced extrasystole. The tachycardia exhibits acceleration during the first four cycles with an oscillation in the fifth and sixth cycles. The recording electrodes contiguous to the stimulating electrodes (RVE1 and RVE2) show continuous fractionated electrical activity throughout the duration of the ventricular tachycardia. In contrast, electrograms RVE3 and LVE show isoelectric interectopic intervals and an increase in the duration of the activation complexes with progressive acceleration of the premature complexes. Disappearance of the fractionated electrical activity in RVE1 and RVE2 is followed immediately by the resumption of a normal rhythm and the return of all electrograms to their control configuration. The morphologic features of the fractionated electrical complexes in both RVE1 and RVE2 show marked variations among successive cycles of the tachycardia. However, the morphologic features of the fractionated activity

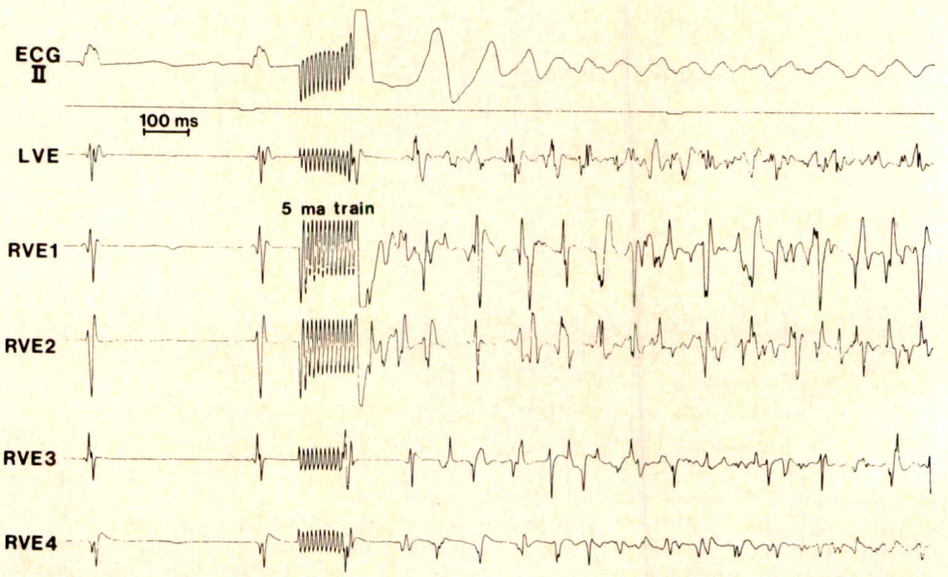


FIGURE 4. Continuous electrical activity evoked by a train of stimuli. Five bipolar electrograms (RVE1, RVE2, RVE3, RVE4 and LVE) are shown with a lead II electrocardiogram. RVE1 and RVE2 were recorded from electrodes placed within 3 mm of the stimulating electrodes. The two other right ventricular electrograms were recorded from electrode pairs placed 8 mm above (RVE4) and 20 mm below (RVE3) the stimulating electrodes. The remaining electrogram (LVE) was recorded from the anterior surface of the left ventricle. After a control cycle, a train of 14 pulses (4 ms, 100 hertz) is delivered to the right ventricle at a current intensity of 5 mA. The train results in a series of accelerating extrasystoles that degenerate into sustained fibrillation. Only the electrodes in close proximity to the stimulating electrodes (RVE1 and RVE2) record continuous electrical activity between the first and second extrasystoles. Once the extrasystoles have degenerated into sustained fibrillations, all of the local electrograms show continuous fractionated electrical complexes.

between the first two extrasystoles are similar to those of the fractionated activity recorded in Figure 3A.

Response to a train of stimuli scanning the T wave: Continuous fractionated electrical activity was also observed when trains of stimuli were used to scan the T wave of the electrocardiogram. Figure 4 shows the development of ventricular fibrillation after the delivery of a 5 mA train of pulses to the right ventricle. The records consist of a surface electrocardiogram (lead II) and five bipolar electrograms. The first two right ventricular electrograms (RVE1 and RVE2) were recorded 3 mm away from the stimulating electrodes, the third and fourth electrograms were recorded 20 mm below (RVE3) and 8 mm above (RVE4) the stimulating electrodes. The two pairs of recording electrodes contiguous to the stimulating electrodes (RVE1 and RVE2) show continuous fractionated electrical activity between the first and second extrasystoles; an isoelectric line is evident in the remote electrograms (LVE, RVE3 and RVE4). Once the initial extrasystoles degenerate into sustained fibrillation, all of the local electrograms display continuous fractionated electrical activity.

When recording electrodes were placed within 2 to 3 mm of the stimulation electrodes (*Fig. 1*) continuous fractionated electrical activity was consistently observed in all animals when either a single stimulus or a train of stimuli was used to evoke multiple extrasystoles or fibrillation. Trains of pulses initiated multiple extrasystoles and fibrillation at lower current intensities than did single pulses. Trains of pulses required an average of 7.0 ± 2.5 mA (±standard deviation) to fibrillate the heart; single stimuli required 15.2 ± 5.4 mA (difference highly significant [$p < 0.01$] by a paired t test). The current intensity needed to evoke multiple extrasystoles and fibrillation also resulted in saturation of the recording amplifiers and long-lasting artifacts (30 to 100 ms) in the bipolar electrograms. To minimize the possibility that the fractionated complexes were artifacts due to amplifier saturation, the coupling intervals of the single stimuli were varied in each animal. Although stimuli delivered after completion of the T wave or during the absolute refractory period were followed by large stimulus artifacts, no continuous fractionated electrical activity was recorded.

Effects of coupling interval on fractionated electrical activity: Figure 5 illustrates the effects of coupling interval on the appearance of fractionated electrical activity at the stimulation site. All records were obtained from the same experiment shown in Figure 4. A control cycle is shown in panel A (cycle length 493 ms). In panel B, a 10 mA stimulus applied to the right ventricle at a coupling interval of 190 ms results in two ventricular extrasystoles. The interval from the onset of the stimulus to the intrinsic deflection of the first extrasystole in RVE3 is 37 ms. Fractionated electrical activity, bridging the interval between the two extrasystoles, is observed only in RVE1 and RVE2. In panel C, the same 10 mA stimulus, delivered earlier in the relative refractory period at a coupling interval of 147 ms, is followed by a single ventricular extrasystole. The interval from the stimulus to the onset of the local activation complex in RVE3 is 87 ms, 45 ms longer than the stimulus-response interval shown in panel B. The longer stimulus-response interval in panel C presumably resulted from extremely slow impulse conduction away from the stimulation site due to excitation of

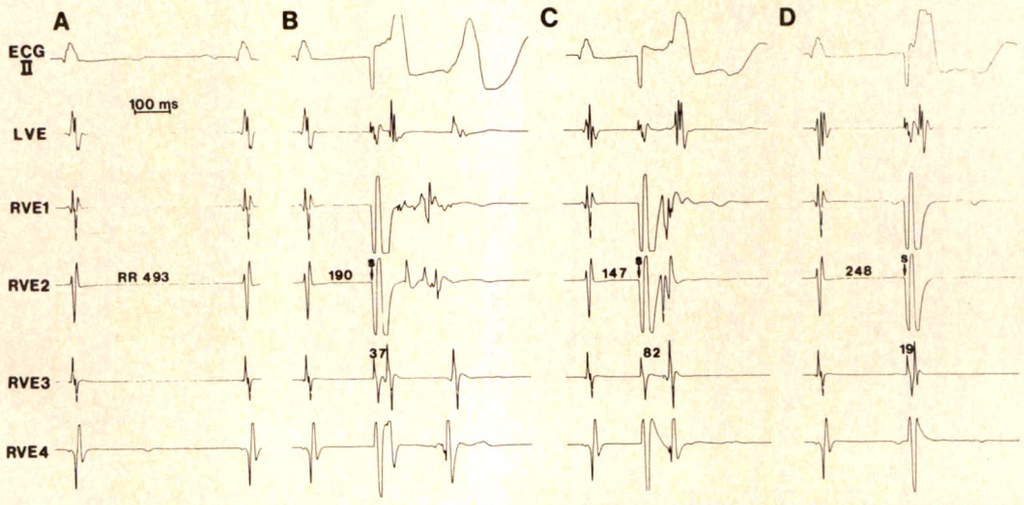


FIGURE 5. Effect of stimulus coupling interval on the appearance of fractionated electrical activity. The electrical recordings shown are identical to those in Figure 4. **A,** a control cycle. **B,** two ventricular extrasystoles in response to a 10 mA stimulus (s) delivered (**arrow**) during the vulnerable period (coupling interval 190 ms). Fractionated electrical activity bridging the interval between the two extrasystoles is apparent only in RVE1 and RVE2. **C,** the same stimulus is delivered earlier in the relative refractory period (coupling interval 147 ms), resulting in only a single ventricular response. The interval from the stimulus to the onset of activation in RVE3 is 82 ms, which is 45 ms longer than the stimulus-response interval in panel B. Although some fractionated electrical activity is recorded in RVE1 and RVE2 the activity disappears shortly after the onset of activation in RVE3 and RVE4. **D,** the 10 mA stimulus is delivered at the end of the T wave (coupling interval 248 ms), resulting in a single premature response. The longer coupling interval, as compared with those in panels B and C, is associated with a shorter stimulus-response interval (19 ms in RVE3). There is no fractionated electrical activity in RVE1 and RVE2 after recovery from the stimulus artifact.

myocardial cells very early in their relative refractory period. Although some fractionated electrical activity is recorded in the RVE1 and RVE2 electrograms immediately after the disappearance of the stimulus artifact, the activity disappears shortly after the onset of activation in RVE3 and RVE4. In panel D, the 10 mA stimulus, delivered at a coupling interval of 248 ms, results in a single ventricular extrasystole. The longer coupling interval in panel D compared with that in panels B and C is associated with a shorter stimulus-response interval (19 ms in RVE3). In contrast to the fractionated electrical activity after the stimulus in panel B, the RVE1 and RVE2 electrograms in panel I return to isoelectric conditions immediately after th stimulus artifact.

Effect of protective zone activation on fraction ated electrical activity: Further evidence indicatin that the fractionated electrical complexes after stimu lation during the vulnerable period were not artifact was provided by the finding that a second stimulu delivered during the protective zone totally abolishe the fractionated activity. Figure 6 illustrates this effe of activation of the protective zone on the productio of fractionated electrical activity. The records consis

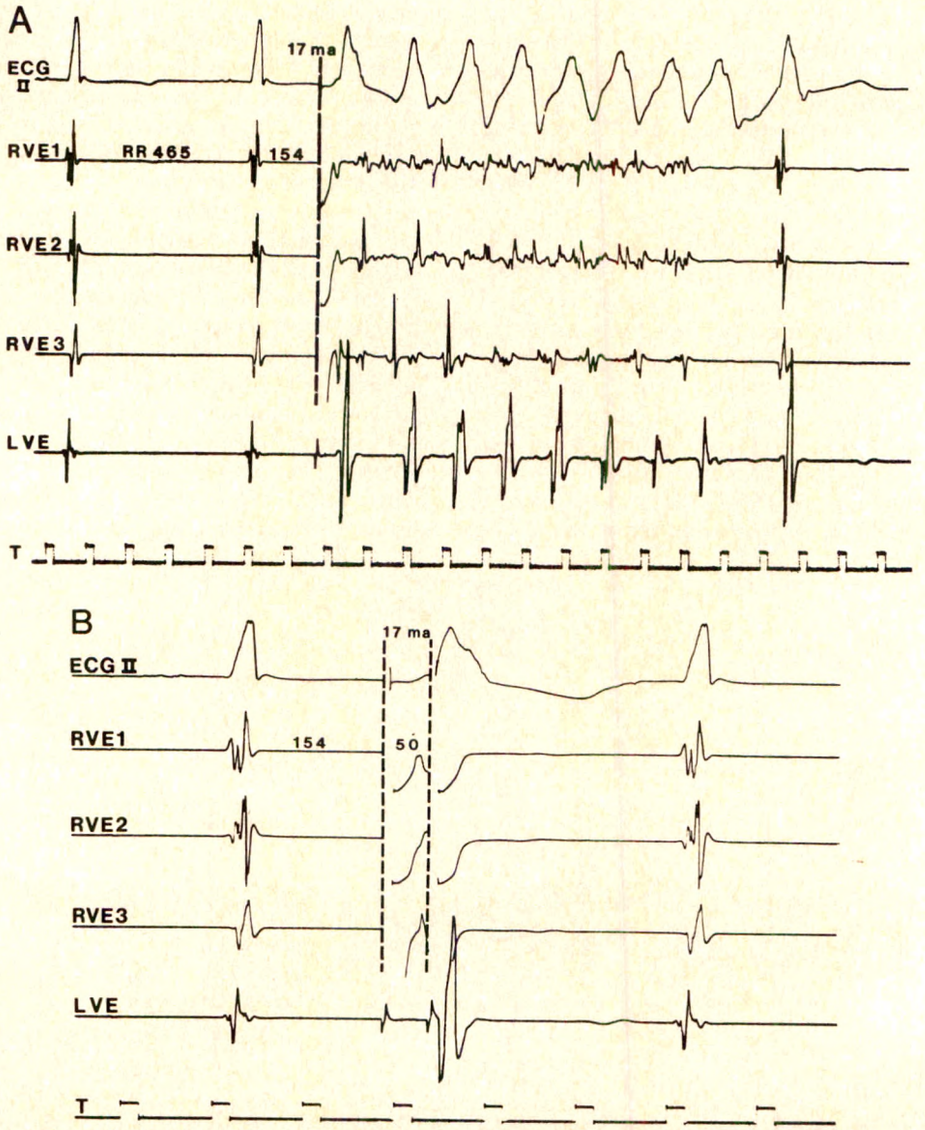


FIGURE 6. Effect of activation of the protective zone on the appearance of continuous electrical activity. The record shows four local electrograms (RVE1, RVE2, RVE3, LVE) and electrocardiographic lead II. The time marks (T) at the bottom of each panel indicate 100 ms intervals. RVE3 was recorded 4 mm below the stimulating electrodes; RVE1 and RVE2 were within 2 mm of the stimulating electrode. LVE was recorded from the anterior left ventricle. **A,** after a control cycle, a 17 mA stimulus (**broken line**) is applied to the right ventricle at a coupling interval of 154 ms. The stimulus results in a short run of ventricular tachycardia that spontaneously terminates after the seventh cycle. Only RVE1 and RVE2 show continuous fractionated electrical activity during the tachycardia. Disappearance of the continuous activity is followed immediately by termination of the tachycardia. **B,** an additional 17 mA stimulus is delivered 50 ms after the same stimulus that produced the repetitive extrasystoles in the left panel. The paper speed in the left panel is 100 mm/s; thus in the right panel is 250 mm/s. Although both stimuli produce large artifacts in the local electrograms there is no trace of fractionated electrical activity extending beyond the single premature response evoked by the stimuli.

of four local electrograms (RVE1, RVE2, RVE3 and LVE) and an electrocardiogram (lead II). Electrogram RVE3 was recorded 4 mm below the stimulating electrodes and RVE1 and RVE2 within 2 mm of the stimulating electrodes. After a control cycle (Fig. 6, left), a 17 mA stimulus is applied to the right ventricle at a coupling interval of 154 ms. The stimulus results in a short run of ventricular tachycardia that spontaneously terminates after the seventh cycle. Continuous fractionated electrical activity is recorded in electrograms RVE1 and RVE2 during the tachycardia; when this activity terminates, the tachycardia also terminates. In the right panel of Figure 6, an additional 17 mA stimulus is delivered 50 ms after an identical stimulus that produced the repetitive extrasystoles and continuous fractionated activity in the left panel. Although both stimuli produce large artifacts in the local electrograms, there is no trace of fractionated electrical activity extending beyond the single premature response evoked by the stimuli.

Discussion

Mechanisms involved in initiation of ventricular fibrillation: Ventricular fibrillation occurs when an organized activation wave front is fractionated into multiple asynchronous wavelets that propagate randomly through the myocardium. The arrhythmia may be induced either by a rapidly discharging automatic focus or by a reentrant circuit. Regardless of the mechanism of induction, fibrillation is sustained by multiple asynchronous reentry.

Although fibrillation is sustained by multiple reentry, the mechanism by which current delivered during the vulnerable period initiates fibrillation has not previously been elucidated. Several studies have indicated that changes in the ventricular fibrillation threshold are closely correlated with the amount of asynchrony in recovery of excitability among adjacent myocardial fibers.[8–12] Furthermore, Spear et al.[12] showed that either a single stimulus or a train of stimuli delivered during the vulnerable period at a central site results in an increase in temporal dispersion in recovery of excitability in tissue adjacent to the central site. They found that increasing the current intensity of either a single pulse or a train of pulses at the central site increased the temporal dispersion of refractoriness at the peripheral sites. They suggested that increasing the intensity of current delivered during the vulnerable period increased the degree of inhomogeneity in recovery of the myocardium until a level was attained that allowed multiple asynchronous reentry and fibrillation.

Although the ventricular fibrillation threshold is affected by interventions that alter the susceptibility of the heart to reentry, no study using direct recordings from the myocardium during the induction of fibrillation has been able to substantiate a reentrant mechanism. Moe et al.[4] suggested that a single stimulus of sufficient intensity delivered during the vulnerable period results in a single rhythmic center from which several impulses are discharged at an accelerating rate. They hypothesized that the progressive decrease in refractory periods associated with the accelerating rate and the conduction delay of the premature responses would establish the conditions necessary for reentry and fibrillation. Their conclusion that the initial accelerating extrasystoles originate from a single rhythmic center was supported by the observation of a similar spread of activation of each extrasystole on the surface and interior of the ventricles. The possibility of a macroreentrant circuit was eliminated because there was a period of time between each of the initial ectopic beats when no area of the ventricles was excited.[4]

Continuous local electrical activity preceding ventricular fibrillation: The results of our study do not support the concept of a single rhythmic center as the mechanism responsible for the genesis of multiple extrasystoles and fibrillation in response to either a single stimulus or a train of stimuli delivered during the vulnerable period. The observation of continuous fractionated electrical activity spanning the interval between the first premature complex and subsequent premature complexes (Figs. 2 to 6) suggests that the mechanism is much more complex than a single accelerating ectopic focus. In the experiments of Moe et al.,[4] electrograms were recorded from very close bipolar electrodes (interelectrode distance 1.5 mm) attached to the ventricles at least 6 mm from the site of stimulation. Presumably their failure to observe continuous fractionated electrical activity resulted from their failure to record from a sufficient mass of tissue in close proximity to the stimulating electrodes. In our experiments (Figs. 2 to 6), fractionated electrical activity was recorded only from wide bipolar electrodes placed very close to the stimulating electrodes. In electrograms recorded several millimeters away from the stimulation site, continuous electrical activity was not evident during the initial extrasystoles but usually appeared once the extrasystoles had degenerated into sustained fibrillation.

Although we were not able to determine the precise origin of the continuous electrical activity recorded in the vicinity of the stimulation site, the amplitude and rate of change of the majority of complexes suggest that they were associated with asynchronous depolarization of local myocardial fibers. Some of the electrical complexes may have been due to asynchronous repolarization of adjacent fibers, although the high pass filters employed presumably attenuated the potentials generated by repolarization to a much greater degree than those generated by depolarization.

It is possible that the continuous fractionated electrical activity recorded after the first extrasystole elicited by a train of stimuli or a single stimulus was not the cause of subsequent spontaneous extrasystoles, but was merely associated with their occurrence. However, the fact that local, fractionated electrical activity always spanned the diastolic interval before the onset of a spontaneous extrasystole argues for a cause and effect relation. In addition, during a run of multiple extrasystoles the disappearance of continuous fractionated electrical activity was followed immediately by the return of a normal rhythm (Fig. 3 and 6). Thus, the ap-

pearance of spontaneous extrasystoles after the initial stimulus-induced extrasystole was probably the result of the formation of multiple local wave fronts outlasting the refractory period of the surrounding myocardium. If the local wave fronts survived long enough, then the multiple extrasystoles degenerated into sustained fibrillation.

Origin of the continuous local electrical activity: Although the continuous fractionated electrical activity is suggestive of reentry, the possibility that multiple ectopic foci were discharging asynchronously must be considered. Moe et al.[4] suggested that a strong stimulus delivered during the vulnerable period creates a local state of tissue polarization that acts as a persisting stimulus resulting in multiple premature responses. In our present experiments, a long-lasting state of polarization created by a train or single stimulus might have produced multiple asynchronous firing of closely adjacent fibers, resulting in the appearance of continuous electrical activity in the local electrograms. However, if the initiation of fibrillation depended on a persisting stimulus due to tissue polarization, it would be difficult to account for the existence of a discrete vulnerable period. As shown in Figure 4, only stimuli delivered during the vulnerable period resulted in local, fractionated electrical activity that preceded the appearance of spontaneous extrasystoles. When stimuli were delivered earlier or later in the cardiac cycle, there was little such activity extending beyond the single premature response evoked by the stimulus.

It is also conceivable that the intense stimulus current could have triggered a series of asynchronous oscillatory afterpotentials in adjacent myocardial fibers, resulting in the appearance of continuous fractionated electrical activity in the local electrograms. However, afterpotentials always follow an action potential[12] and would not occur until after completion of the first premature action potential evoked by the stimulus. In our study, fractionated continuous electrical activity appeared immediately after the disappearance of the stimulus artifact, 30 to 100 ms after the delivery of the stimulus current. It is doubtful that the interval between the stimulus and the onset of continuous activity would be sufficient for completion of an action potential and generation of an afterpotential. Thus, our results suggest that both the initiation and the maintenance of fibrillation are due to local reentry.

Protective zone: Verrier et al.[13] found that in addition to a discrete vulnerable period, there is a discrete protective zone. This protective zone begins 10 to 15 ms after the nadir of the vulnerable period and has a duration of approximately 50 ms. A stimulus delivered during this time will prevent the development of fibrillation in response to a stimulus delivered during the vulnerable period. Activation of the protective zone in our study consistently abolished the continuous electrical activity that preceded the development of spontaneous extrasystoles and fibrillation. The protective zone occurs at a time when reentrant activity should be confined to a small mass of tissue in the immediate vicinity of the stimulation site. Thus, a strong stimulus delivered during this time could block reentry by depolarizing unexcited fibers in the circuit.

Comparison of fibrillation threshold techniques: The current required to produce continuous electrical activity and fibrillation with a train of pulses in our study was consistently less than that required for a single pulse. These observations are consistent with the lower fibrillation threshold that has been reported for a train of pulses.[14,15] The lower current level required for a train of pulses to initiate reentrant excitation may be due to complex interactions between individual pulses in a train.[15] Also, the current required for fibrillation when a train of pulses is used may depend on the timing of the pulses relative to the protective zone.[14] Furthermore, the discrepancy in the amount of current necessary to evoke fibrillation with the two techniques may depend largely on liberation of local stores of catecholamines by the stimuli. Euler[14] found that the elevation of the ventricular fibrillation threshold for a train of pulses in response to doses of propranolol sufficient to produce beta adrenergic blockade is seven-fold greater than the elevation in the threshold obtained with the single pulse technique. It is probable that the locally released stores of catecholamines increase the asynchrony in recovery of excitability of tissue adjacent to the stimulating electrodes, thereby facilitating the likelihood of reentry. Regardless of the precise mechanisms that result in the lower fibrillation threshold with a train of pulses than with a single pulse, the appearance of continuous fractionated electrical activity close to the stimulation site suggests that both methods initiate fibrillation by local reentry.

Acknowledgment

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Electrophysiologic Effects of Disopyramide Phosphate on Reentrant Ventricular Arrhythmia in Conscious Dogs After Myocardial Infarction

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The electrophysiologic actions of disopyramide phosphate on reentrant ventricular tachycardia induced by premature ventricular stimuli were evaluated in conscious dogs 2 to 4 days after myocardial infarction. Disopyramide was administered as a series of intravenous infusions to obtain successive steady state plasma disopyramide concentrations of 1.02 ± 0.02, 2.05 ± 0.08, 3.94 ± 0.09 and 7.69 ± 0.18 μg/ml (mean values ± standard error of the mean). Disopyramide plasma concentrations of 1.02 ± 0.02 μg/ml produced an increase in the rate and duration of ventricular tachycardia as well as in the interval during which premature ventricular stimuli produced ventricular tachycardia. The effective refractory period of normal myocardium was decreased and conduction (activation time) was improved in ischemic myocardium. Increasing steady state plasma disopyramide concentrations slowed the rate of ventricular tachycardia without decreasing its duration. Slowing of the rate of tachycardia occurred simultaneously with a depression of conduction in normal and ischemic myocardium and an increase in ventricular refractoriness. Induction of ventricular tachycardia was prevented only at steady state plasma disopyramide concentrations of 7.69 ± 0.18 μg/ml. The results of this study suggest that subtherapeutic plasma concentrations of disopyramide may facilitate the development of reentrant ventricular arrhythmia in the electrically unstable heart. Ventricular tachycardia or fibrillation, or both, may be prevented only by plasma disopyramide concentrations that are in excess of the normal therapeutic range of 2 to 4 μg/ml.

Sudden death in patients with coronary artery disease results from severe disturbances of cardiac impulse formation or conduction that most often lead to ventricular fibrillation. Continuous electrical instability of the ischemic heart has been suggested as the primary factor leading to cardiac rhythm disturbances and can be exposed by the introduction of a critically timed premature ventricular stimulus that will initiate sustained ventricular tachycardia or ventricular fibrillation, or both.[1–5]

Studies of drugs that will prevent reentrant ventricular arrhythmia have been extensive in recent years, but have been hampered by the lack of a suitable animal model capable of identifying pharmacologic agents with the ability to reduce the incidence of ventricular fibrillation in the chronically ischemic heart. In most animal models used in the study of antiarrhythmic drugs, myocardial ischemia is created by acute coronary arterial ligation. Although this procedure will lead to ventricular fibrillation in a large proportion of the trials, the electrical events do not simulate the chronic electrical instability associated with sudden coronary death.[6] In addition, ventricular tachycardia present 24 to 48 hours after experimental coronary arterial occlusion rarely culminates in ventricular fibrillation and is believed to be due to enhanced automa-

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ticity in Purkinje fibers.[6,7] Recently, it was demonstrated that a critically timed electrically induced premature ventricular stimulus could initiate reentrant ventricular tachyarrythmia and ventricular fibrillation in dogs 2 to 9 days after acute myocardial infarction. This reentrant electrical activity also simulated that observed in patients in whom reentrant rhythms could be induced by programmed electrical stimulation of the heart.[8,9]

This study was undertaken for the purpose of evaluating the ability of disopyramide phosphate to prevent reentrant arrhythmia resulting from programmed electrical stimulation in the presence of chronic myocardial ischemia. The electrophysiologic effects of disopyramide phosphate were evaluated in relation to drug plasma concentrations. The results of these studies in the conscious dog with experimentally induced chronic myocardial ischemia demonstrate that disopyramide in clinically recommended plasma concentrations (2 to 4 μg/ml) is unlikely to be beneficial in preventing reentrant ventricular tachyarrhythmia; this prevention can only be accomplished with plasma concentrations in excess of 4 μg/ml.

Methods

Animal preparation: Male mongrel dogs weighing between 14.2 and 18.0 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg body weight. Each animal was intubated with a cuffed endotracheal tube and ventilated with room air using a Harvard respirator. With use of aseptic techniques, sterile catheters were implanted in the left common carotid artery and left external jugular vein and passed subcutaneously to the surface through an incision in the back of the neck. A left thoracotomy was performed in the fourth intercostal space and the heart was suspended in a pericardial cradle. A 5 mm section of the left anterior descending coronary artery was dissected free from the surrounding myocardium at the tip of the left atrial appendage. A length of suture was passed around the artery and a 20 gauge needle, then securely tied and the needle withdrawn. Left anterior descending coronary arterial flow was monitored using an electromagnetic flow probe (Carolina Medical Electronics) before and after stenosis to ensure that coronary flow at rest was undisturbed. Silastic® tubing was used to occlude coronary flow for a period of 90 minutes and then flow was allowed to return through the stenosed artery. Lidocaine hydrochloride, 5 mg/kg intravenously followed by 5 mg/kg intramuscularly, was given to those animals manifesting severe ventricular arrhythmia on reinstitution of coronary flow.

Electrical placements: A bipolar electrode was sewn onto the surface of the left atrial appendage. A second bipolar plunge electrode (28 gauge stainless steel, 5 to 7 mm in length) was placed on the right ventricular outflow tract with the exposed electrode tips placed in the interventricular septum.

Bipolar composite electrodes were placed on the epicardial surface of the left ventricle. One bipolar composite electrode was placed over normal myocardium and the second was placed over ischemic and infarcted myocardium. Correct placement of the bipolar composite electrodes was established at autopsy. The electrode wires were exited through the chest and passed subcutaneously to the back of the neck. The chest was closed in layers and procaine penicillin G, 1.2 million units, was administered intramuscularly.

Electrophysiologic studies: Forty-eight hours after myocardial infarction, the animals were conscious and resting comfortably, supported in a sling. Arterial pressure was monitored with a Statham P23DC pressure transducer and recorded on a Grass model 7 polygraph. A lead II electrocardiogram was monitored continuously and recorded. Bipolar composite electrograms, an atrial bipolar electrogram and a lead II electrocardiogram were recorded on a Honeywell model 1858 Visicorder filtered at 15 to 2,500 hertz. If the ventricular ectopic rate was greater than 10 beats/min, the animal was returned to its quarters and monitored 24 hours later. If the rate was 10 beats/min or less, the following procedure was used: A Grass model SD_5 stimulator was used to deliver square wave impulses, 3 ms in duration, at a voltage twice the diastolic threshold for atrial or ventricular pacing (S_1 stimuli). A Tektronix model 565 oscilloscope and differential amplifier were used to trigger the output of a Grass model S88 stimulator at the peak of the R wave of the lead II electrocardiogram. A Grass model S88 stimulator and SIU5 stimulus isolation unit delivered 3 ms square wave pulses (S_2 and S_3 stimuli) at selected delays after the peak of the R wave to the bipolar electrode located in the interventricular septum. Diastolic threshold was determined 200 ms after the peak of the R wave. All subsequent premature stimuli delivered to the interventricular septum were 1.5 times diastolic threshold.

The effective refractory period of the left ventricular myocardium was determined using square wave pulses (1.5 times threshold, 3 ms in duration) and decreasing the R to S_2 interval until a conducted beat was not generated. Activation times (Q-EG intervals), the delay from the Q wave of the lead II electrocardiogram to the major positive spike of the normal zone or ischemic zone epicardial bipolar composite electrograms, were determined during atrial pacing at a rate of 175 beats/min. All electrophysiologic measurements were made from recordings performed at a paper speed of 100 to 400 mm/s.

Administration of disopyramide: Disopyramide phosphate was administered by a series of two stage intravenous infusions as described by Wagner.[10] The values for apparent volume of distribution (2.01 liters/kg), alpha phase elimination constant (44.4 $hour^{-1}$), and beta phase elimination constant (0.55 $hour^{-1}$) were obtained from earlier pharmacokinetic studies.[11,12] The infusion protocol was designed to reach and maintain successive steady state disopyramide plasma levels of 1, 2, 3, 4, and 8 μg/ml. An infusion of disopyramide at a rate of 23.3 mg/kg per hour for 4 minutes was followed by a second infusion of 1.09 mg/kg per hour designed to maintain plasma disopyramide concentrations of 1 μg/ml. The infusion rate was increased to 24.4 mg/kg per hour for 4.0 minutes followed by an infusion at a rate of 2.18 mg/kg per hour to maintain plasma concentrations of 2 μg/ml. The infusion rate was increased again to 24.4 mg/kg per hour for 4.8 minutes followed by an infusion at a rate of 3.28 mg/kg per hour to maintain plasma concentrations of 3 μg/ml. To increase the steady state plasma concentrations to 4 μg/ml, the infusion rate was increased to 24.4 mg/kg per hour for 5.3 minutes followed by an infusion at a rate of 4.37 mg/kg per hour to maintain steady state concentrations. Steady state plasma disopyramide concentrations of 8 μg/ml were achieved by increasing the infusion rate to 101.9 mg/kg per hour for 5 minutes followed by an infusion at a rate of 8.72 mg/kg per hour. A period of 20 minutes was allowed to pass at each steady state plasma concentration before electrophysiologic testing was initiated. Disopyramide phosphate was administered using a Harvard model 975 infusion pump.

Determination of plasma disopyramide concentration: Blood samples (3 ml) were collected in 5 ml tubes containing 500 units of sodium heparin. Plasma disopyramide concentrations were determined with the gas chromatographic method of Patterson et al.[13] Plasma samples were taken just

before and after electrophysiologic testing at each steady state plasma level. Plasma potassium concentrations were determined from these samples with use of flame spectrophotometry.

Determination of infarct size: The animals were anesthetized with sodium pentobarbital, 20 mg/kg intravenously. The heart was excised, rinsed briefly in cold water and sliced from apex to base into 1 cm thick sections. The slices were incubated in 0.2 percent triphenyltetrazolium in 0.1 *M* phosphate buffer, pH 7.4, at 40°C for 15 minutes. Infarct size was determined gravimetrically and expressed as a percent of total left ventricular mass.

Materials: Disopyramide phosphate and p-chlorodisopyramide phosphate were obtained from the G.D. Searle Company. Triphenyltetrazolium was purchased from the Sigma Chemical Company. All other chemicals were reagent grade.

Statistical methods: Numerical values are expressed as the mean ± standard error of the mean. Differences between groups were analyzed by analysis of variance.

Results

Rate-dependent conduction disorders: Two to 4 days after myocardial infarction, the ventricular ectopic rate had decreased to 3 ± 1 complexes/min, and the animals were entered into the study protocol. Composite bipolar electrodes were used to record left ventricular myocardial activation. Activation of ischemic myocardium was prolonged (82 ± 13 ms) compared with activation of normal myocardium (49 ± 11 ms) (Table I). Left atrial pacing was used to increase sequentially the ventricular rate to 300 beats/min or until the development of atrioventricular dissociation. As the ventricular rate increased, there was a significant increase in the duration of activation of ischemic myocardium whereas no change was seen in the duration of electrical activity in normal left ventricular myocardium (Table I). A further increase in the ventricular rate produced fractionation of the ischemic zone bipolar composite electrogram (Fig. 1).

Induction of ventricular tachycardia: Two to 4 days after myocardial infarction, programmed electrical stimulation was used to initiate reentrant rhythm in the conscious dogs. Premature ventricular stimuli were introduced during both normal sinus rhythm (cycle lengths 357 to 501 ms) and atrial pacing (cycle lengths 284 to 454 ms). No differences were observed between the duration or rate of ventricular tachycardia induced in any one animal by single or double premature stimul during either normal sinus rhythm or atrial pacing, anc therefore the data are grouped in Table II. In thre animals, sustained ventricular tachycardia lasting i excess of 2 minutes was observed. Four of eight episode were self-terminating. Episodes of sustained ventricula tachycardia producing hypotension were terminate with single premature ventricular stimuli (Fig. 2). In on animal, ventricular tachycardia proceeded to ventric ular fibrillation within 10 seconds of introduction of a single premature stimulus.

Electrophysiologic effects of steady state plasma disopyramide concentrations of 1 μg/ml: Disopyramide plasma concentrations of 1.02 ± 0.02 μg/ml increased both the rate and duration of the induced ventricular tachycardia and duration of ischemic zone asynchronous electrical activity (Table II, Fig. 3 and 4). The interval during which ventricular tachycardia could be induced (induction period) also was increased. The critical coupling interval was increased for ventricular tachycardia induced by single (S_2) or double (S_2 and S_3) premature stimuli. Sustained ventricular tachycardia now could be induced in two animals in which only nonsustained ventricular tachycardia could be induced before administration of disopyramide. The changes occurred simultaneously with a decrease in the ventricular effective refractory period and a decrease in activation times of the ischemic myocardium (Table III). However, the cycle lengths at which Wenckebach-like conduction of ischemic potentials occurred

TABLE I

Duration of Electrical Activation of Ventricular Myocardium 48 Hours After Myocardial Infarction

Cycle Length (ms)	Duration of Activation (ms)	
	Normal Zone	Ischemic Zone
430 ± 23	49 ± 11	82 ± 13†
253 ± 12	46 ± 8	106 ± 19*

*,† Probability [p] values: * <0.05, compared with ischemic zone electrical activation duration at a cycle length of 430 ± 23 ms, † <0.05 compared with normal zone.

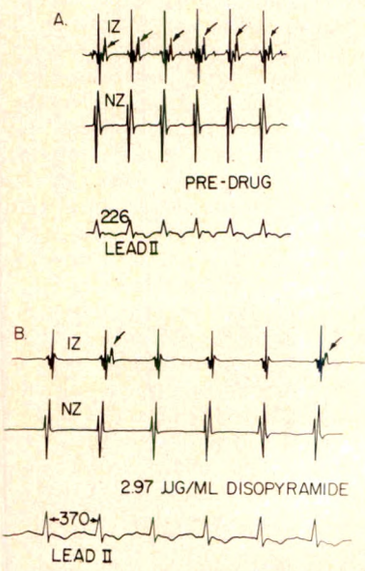


FIGURE 1. Conduction in ischemic myocardium—effect of disopyramide. **A,** before administration of disopyramide, atrial pacing decreases the ventricular cycle length to 226 ms; at this cycle length, fractionation of ventricular activation occurs. Slightly shorter cycle lengths produced Wenckebach-like conduction of these ischemic potentials (not shown). **B,** at disopyramide plasma concentrations of 2.97 μg/ml, Wenckebach-like conduction (3:1) occurs at a cycle length of 370 ms. Ischemic electrical potentials are marked by **arrows.** IZ = ischemic zone; NZ = normal zone.

TABLE II

Electrophysiologic Variables

Plasma Disopyramide Concentration (μg/ml)	Reentrant Beats (n)	Cycle Length of Ventricular Tachycardia (ms)	Duration of Asynchronous Activity (ms)	Induction Period (ms)	
				S_2	S_3
(before drug administration)	6.2 ± 0.8	163 ± 6	1005 ± 83	25 ± 2	37 ± 4
1.02 ± 0.02	8.4 ± 0.8*	155 ± 2*	1195 ± 87*	42 ± 4*	48 ± 4*
2.05 ± 0.08	5.5 ± 0.8	193 ± 8*	990 ± 81	24 ± 6	34 ± 4
2.99 ± 0.03	4.3 ± 1.1*	218 ± 14†	968 ± 123	20 ± 5	26 ± 7*
3.94 ± 0.09	3.6 ± 0.4†	245 ± 8†	882 ± 102*	16 ± 5*	23 ± 9*
7.69 ± 0.18	0.6 ± 0.5†	315 ± 10†	—	—	—

* $p < 0.05$, † $p < 0.01$ compared with values before drug administration.

were not altered from the values before drug administration.

Electrophysiologic effects of increasing plasma disopyramide concentrations: Plasma disopyramide concentrations were increased sequentially to steady state concentrations of 2.05 ± 0.08, 2.99 ± 0.03, 3.94 ± 0.09 and 7.69 ± 0.18 μg/ml. These increases produced a concentration-dependent increase in the cycle length of ventricular tachycardia without shortening the duration of the tachycardia until plasma levels of 7.69 ± 0.18 μg/ml were attained (Table II, Fig. 3 and 4). The induction periods for the premature stimuli S_2 and S_3 were reduced sequentially by increasing plasma disopyramide concentrations, although ventricular tachycardia could be induced in all animals at plasma disopyramide concentrations of 3.94 ± 0.09 μg/ml. The slowing of the rate of tachycardia occurred simultaneously with the depression of cardiac conduction, as reflected in the concentration-dependent increase in the cycle length of the ventricular arrhythmia and the increase in the activation times of normal and ischemic myocardium. Increasing plasma disopyramide concentrations also produced sequential increases in ventricular refractoriness (Table III).

Disopyramide plasma concentrations of 7.69 ± 0.18 μg/ml were necessary to suppress completely the induction of ventricular tachycardia. In several instances, single or double reentrant beats were seen (Fig. 3), but longer runs of ventricular tachycardia could not be induced. The elevated disopyramide plasma concentration produced considerable conduction delay in normal and ischemic myocardium and produced a 23 ms increase in the effective refractory period of the normal left ventricular myocardium (Table III).

Plasma potassium concentrations: Plasma potassium concentrations were determined before and after electrophysiologic testing at each steady state plasma disopyramide concentration as well as before adminis-

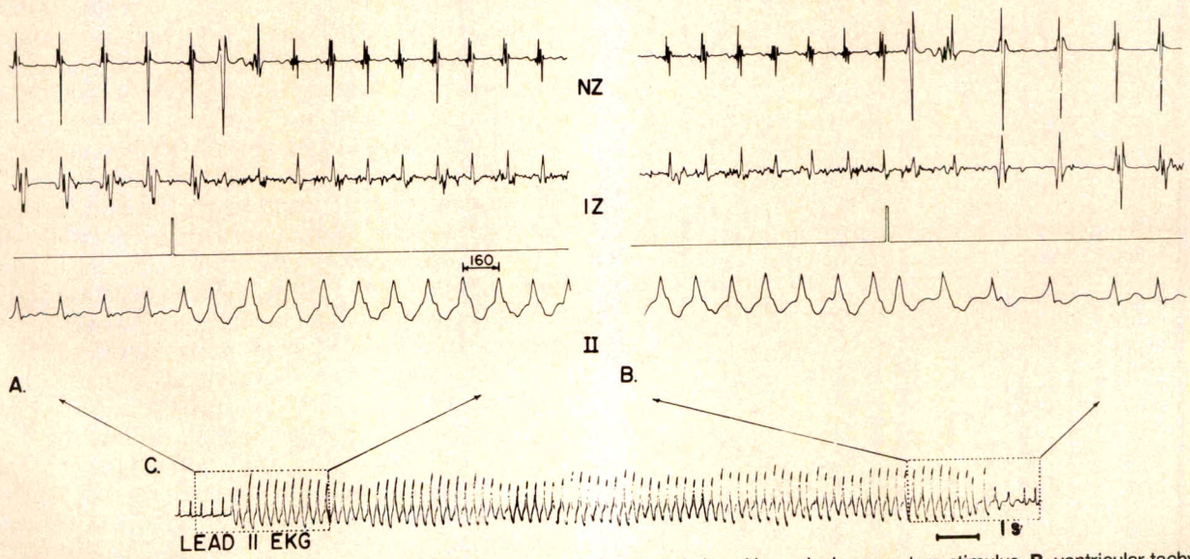


FIGURE 2. Sustained ventricular tachycardia. **A,** sustained ventricular tachycardia is induced by a single premature stimulus. **B,** ventricular tachycardia is terminated by a single premature impulse because of hypotension. Premature stimuli are marked by **narrow rectangles** in **A** and **B.** Electrical activation of normal myocardium (NZ) remains discrete during ventricular tachycardia although ischemic zone (IZ) activation was continuous. Activation of normal and ischemic myocardium was measured with bipolar composite electrodes. EKG = electrocardiogram.

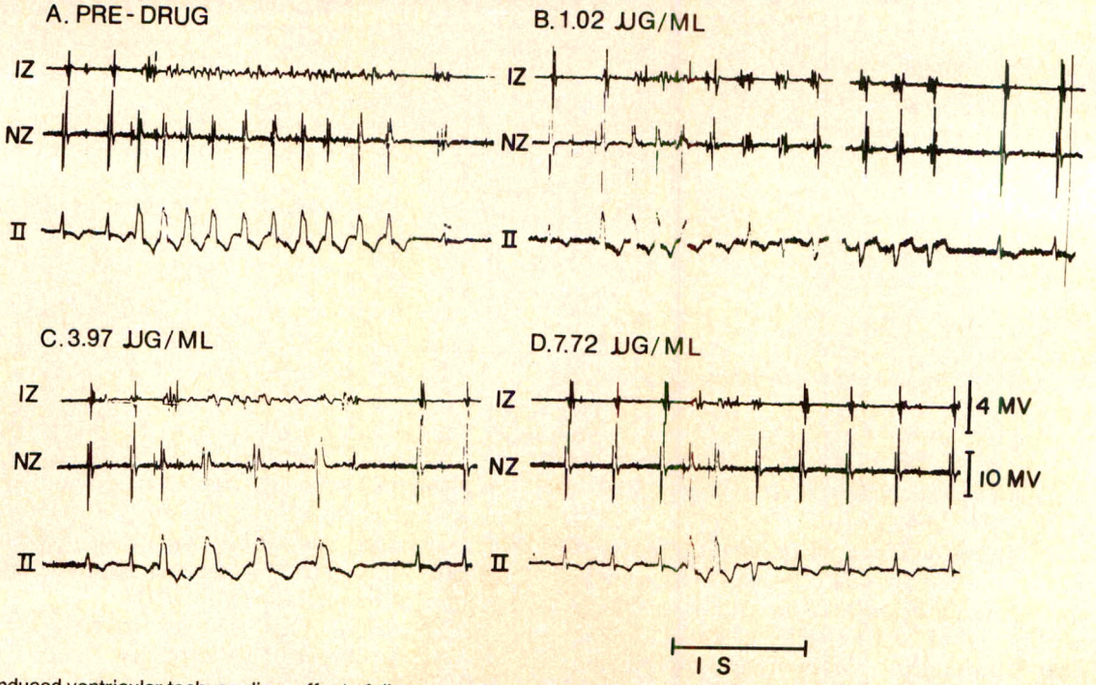


FIGURE 3. Induced ventricular tachycardia—effect of disopyramide. **A,** before administration of disopyramide, a single premature stimulus elicits a nine beat ventricular tachycardia with a cycle length of 225 ms. **B,** at a plasma disopyramide concentration of 1.02 μg/ml, a single premature stimulus produces sustained ventricular tachycardia at a cycle length of 216 ms. The ventricular tachycardia was sustained for 2 minutes and 45 seconds, after which spontaneous slowing and termination were seen. **C,** at a plasma disopyramide concentration of 3.97 μg/ml, a single premature stimulus elicits a ventricular tachycardia of three beats having a cycle length of 419 ms. **D,** at a plasma disopyramide concentration of 7.72 μg/ml, two premature stimuli produce a single reentrant beat. Activation of normal myocardium (NZ) remained discrete in the composite electrogram whereas ischemic zone activation (IZ) was continuous during ventricular tachycardia.

tration of disopyramide. Before administration of disopyramide, the plasma potassium concentration was 3.8 ± 0.1 mEq/liter and did not change significantly throughout the course of the experiment.

Infarct size: Occlusion of the left anterior descending coronary artery for a period of 90 minutes followed by reperfusion of the ischemic myocardium produced infarct masses of 3.2 to 34.6 g, representing 3.0 to 34.0 percent of the left ventricular mass (mean 19.4 ± 3.8 percent). The infarcts were located subendocardially and did not extend to the epicardial surface.

TABLE III

Effective Refractory Periods and Changes in Q-EG Interval (mean values ± standard error of the mean)

Plasma Disopyramide Concentration (μg/ml)	Effective Refractory Periods (ms)	ΔQ-EG (ms)	
		Normal Zone	Ischemic Zone
(before drug administration)	142 ± 8	...	...
1.02 ± 0.02	138 ± 9*	−0.2 ± 0.3	−3.9 ± 1.6*
2.05 ± 0.08	146 ± 8*	0.2 ± 0.3	4.2 ± 0.9*
2.99 ± 0.03	147 ± 9*	0.6 ± 0.2*	7.6 ± 1.2*
3.94 ± 0.09	148 ± 10*	1.9 ± 0.6*	9.8 ± 0.9†
7.69 ± 0.18	165 ± 3†	4.6 ± 0.7*	18.5 ± 2.9†

* $p < 0.05$, † $p < 0.01$ compared with values before drug administration.

Q-EG = interval from the initiation of the Q wave of lead II to the major deflection in the bipolar electrogram; ΔQ-EG = change from the value obtained before drug administration (value before drug administration = 0).

Discussion

Improved activation in ischemic myocardium and induction of reentrant tachyarrhythmia with subtherapeutic concentrations: Steady state plasma disopyramide concentrations of 1.02 ± 0.02 μg/ml increased the duration and decreased the cycle length of reentrant ventricular tachycardia. This action is not unique to disopyramide: El-Sherif and Lazzara[14] have shown verapamil to improve conduction in ischemic canine myocardium by improving depressed phase 0 maximal upstroke velocity of Purkinje fibers. In addition, verapamil has been shown to decrease the cycle length of reentrant ventricular tachycardia and to increase the incidence of ventricular fibrillation in dogs 3 to 5 days after myocardial ischemic injury.[15] Although there are few similarities in the mechanisms of action of disopyramide and verapamil, these data suggest that improvement of depressed conduction in ischemic myocardium may result in increased rates of ventricular tachycardia and an increased incidence of ventricular fibrillation.

Reddy and co-workers[16,17] demonstrated that subtherapeutic concentrations of procainamide facilitated the induction of tachyarrhythmia in human subjects. Nonsustained ventricular tachycardia became sustained

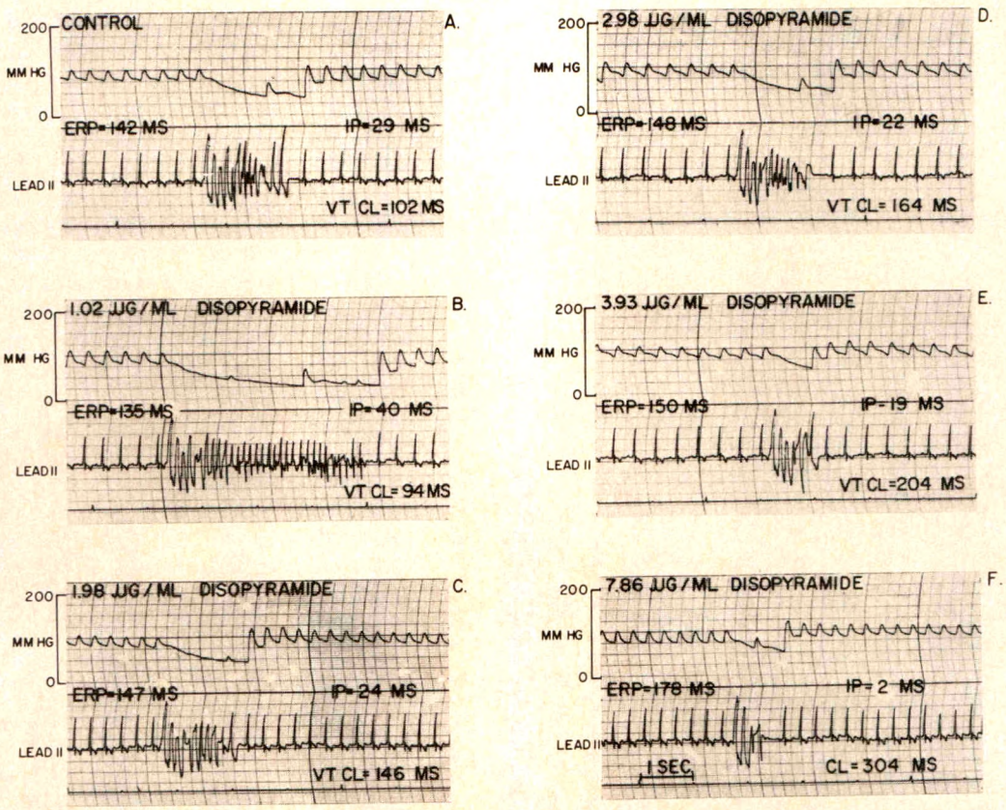


FIGURE 4. Induced ventricular tachycardia—effect of disopyramide. Lead II electrocardiograms and arterial blood pressure tracings are shown before and after administration of disopyramide. **A,** double premature stimuli produce a 10 beat run of ventricular tachycardia with a cycle length (VT CL) of 102 ms. **B,** at a plasma disopyramide concentration of 1.02 μg/ml, the tachycardia increases to 20 beats at a cycle length of 94 ms after two premature stimuli. The period of induction of tachycardia (IP) increases from 29 to 40 ms whereas the effective refractory periods (ERP) is reduced from 142 to 135 ms. **C,D,E,** increasing plasma disopyramide concentrations of 1.98, 2.98 and 3.93 μg/ml produce lengthening of the cycle lengths of the induced ventricular tachycardia to 146, 164 and 204 ms, respectively, and decrease the duration of the ventricular tachycardia. Only modest reductions of the induction periods and small increases in the effective refractory periods are seen. **F,** two premature stimuli produce a reentrant couplet with a cycle length of 304 ms. The induction period of this couplet was 2 ms.

after administration of procainamide, and reentrant rhythms could be induced only after its administration. Horowitz et al.[18] observed similar results when they administered procainamide to survivors of apparent sudden coronary death whose nonsustained reentrant rhythm became sustained ventricular tachycardia. They reported that a decrease in conduction velocity occurred simultaneously with facilitated reentry and postulated that procainamide facilitated reentry by slowing conduction velocity to a greater degree than it increased ventricular refractoriness. Larger doses of procainamide prevented the induction of reentrant cardiac rhythms. In our study with disopyramide, depression of cardiac conduction was not observed at the time when the periods required for induction of reentrant rhythms were increased; rather, there was an improvement in myocardial activation in ischemic myocardium.

The electrophysiologic actions of subtherapeutic concentrations of disopyramide have not previously been investigated. However, "therapeutic concentrations" of disopyramide have been shown to produce decreases in the rate of phase 0 depolarization of canine Purkinje fibers[19–21] and in myocardial conduction velocity.[22] Improvement in cardiac conduction has not been reported. The direct depressant actions of disopyramide may predominate at higher concentrations whereas at lower concentrations the drug might act indirectly through an antagonism of muscarinic cholinergic receptors.[22–25]

Increased activation time and ventricular refractoriness with high plasma concentrations: Increasing plasma concentrations of disopyramide produced progressive increases in ventricular activation times and in ventricular refractoriness in normal and ischemic myocardium. The increases in activation times of ischemic myocardium were greater than those in normal myocardium. Slowing of the cardiac impulse through ventricular myocardium comprising the reentry circuit is a possible factor involved in the slowing of the ventricular tachycardia after administration of disopyramide, although the role of increased myocardial refractoriness is unknown.

Increasing steady state disopyramide plasma concentrations slightly reduced the periods required for induction of ventricular tachycardia. Reduction of this critical interval may be somewhat beneficial, but com-

plete prevention of the induction of ventricular tachycardia may be necessary for prevention of sudden coronary death. Ruskin and Garan[26] demonstrated that antiarrhythmic drug therapy that renders ventricular tachycardia noninducible by programmed cardiac stimulation constitutes effective prophylaxis against spontaneous recurrent sustained ventricular tachycardia in the majority of patients studied. Josephson et al.[27] showed that failure to maintain plasma concentrations of antiarrhythmic drugs at levels previously shown to be effective in preventing the induction of sustained ventricular tachycardia can lead to the recurrence of sustained ventricular tachycardia or sudden coronary death. The 25 to 40 percent reduction in the period required for induction of sustained tachycardia, seen in our study at plasma disopyramide concentrations of 3.94 ± 0.09 μg/ml, may be ineffective in preventing sudden coronary death because only concentrations of 7.69 ± 0.18 μg/ml prevented electrical induction of ventricular tachyarrhythmia (Table II).

It is not surprising that high plasma disopyramide concentrations are needed for suppression of induction of ventricular tachycardia. Benditt et al.[28] reported that disopyramide plasma concentrations that prevented the induction of ventricular tachycardia in human subjects were in excess of 3 μg/ml (mean nearly 5 μg/ml). Similarly, procainamide's effectiveness was reported to require plasma concentrations in excess of 9 μg/ml whereas quinidine plasma concentrations necessary for prevention of induction of ventricular tachycardia were in excess of 3 μg/ml.[25–27] Thus, the plasma concentrations of antiarrhythmic agents necessary for prevention of sudden coronary death may be higher than currently accepted "therapeutic concentrations." However the "high" plasma concentrations of antiarrhythmic drugs may prove to have deleterious actions on cardiac electrophysiology and myocardial function.[29–31]

Clinical implications: The majority of cardiac deaths are sudden and most likely due to a "primary" arrhythmic event most often characterized by ventricular fibrillation. Endeavors to prevent sudden coronary death with pharmacologic means have resulted in numerous reports in which drugs have been claimed to be "effective" solely because of their ability to reduce the frequency of premature ventricular complexes. This study, although conducted in the experimental animal, might provide some important insights into an understanding of why there often exists a lack of a predictable relation between the ability to suppress chronic asymptomatic complex ventricular arrhythmia and ventricular fibrillation or sudden coronary death. As demonstrated in the canine model using programmed cardiac stimulation in the presence of latent electrical instability, concentrations (2 to 4 μg/ml) of disopyramide known to reduce or prevent complex premature depolarizations were unable to prevent the induction of sustained reentrant ventricular tachyarrhythmia. The suggestion that recurrent episodes of ventricular tachycardia or ventricular fibrillation, or both, might be prevented by relatively high plasma concentrations of disopyramide has important implications with respect to future clinical trials designed to explore the prophylactic use of this drug in the patient at risk of sudden coronary death. A beneficial effect might not be realized if such trials follow current "therapeutic" guidelines in suggesting maintenance of plasma concentrations of 2 to 4 μg/ml. However, the negative inotropic effect of disopyramide may preclude the use of higher dosage regimens in patients with compromised left ventricular function.

We are entering an era in which the pharmacologic prevention of sudden coronary death may soon become a reality. The task of identifying the proper agent or agents will not be a simple one; a single approach to the prevention of ventricular fibrillation is probably not attainable because the arrhythmia probably results from the interplay of many mechanisms, the most important of which is an acute or chronic state of electrical instability. The animal model used in our study has the advantage over previous models of more closely representing the clinical state associated with sudden coronary death. It may be useful in exploring the pathophysiologic processes that render the myocardium vulnerable to ventricular fibrillation and in studying how pharmacologic agents act to prevent a fatal electrical event.

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The No Reflow Phenomenon: A Time-Limiting Factor for Reperfusion After Coronary Occlusion?

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A study was performed in 33 dogs to ascertain (1) whether the "no reflow" phenomenon is a critical factor determining the time beyond which revascularization can no longer salvage ischemic myocardium, and (2) whether reperfusion damages tissue not otherwise destined to become necrotic. Twelve dogs were subjected to 2 hours of coronary occlusion followed by 4 hours of reperfusion, 10 dogs to 4 hours of occlusion followed by 2 hours of reperfusion and 11 dogs to 6 hours of coronary occlusion alone. The area of "no reflow" was determined by injecting a fluorescent dye into the left atrium at the end of 6 hours with the coronary artery patent, and the ischemic area at risk by injecting methylene blue dye into the left atrium with the coronary artery reoccluded. The area of necrosis on all 5 mm transverse ventricular sections was determined by incubation in triphenyltetrazolium chloride stain and compared with its respective area at risk and area of no reflow. In all dogs the no reflow area was always significantly smaller than, and contained topographically within, the area of necrosis. Furthermore, the area of necrosis expressed as a percent of the area at risk was significantly smaller for dogs with 2 or 4 hours of occlusion and reperfusion than for dogs with longer periods of occlusion and briefer periods of reperfusion. It is concluded that (1) the no reflow phenomenon does not determine the critical time for salvageability of myocardium by revascularization because the area of no reflow is surrounded by necrotic but reperfusable tissue, and (2) reperfusion does not increase the quantity of ischemic tissue that becomes necrotic.

During the last decade many interventions have been shown experimentally to protect ischemic myocardium from necrosis.[1–3] One of the most attractive of these experimental methods is early reperfusion because it has direct application to treatment of clinical myocardial ischemia with coronary vasodilator agents,[4] intracoronary streptokinase administration and coronary arterial bypass grafting.[5] A potentially important complicating aspect of early reperfusion is the "no reflow" phenomenon, which has been defined in the canine heart as a region of myocardium that does not allow normal reflow of blood during reperfusion after experimental coronary occlusion of 90 minutes or longer.[6] The no reflow phenomenon is one of several controversial issues concerning reperfusion, all related to whether early reperfusion is beneficial to ischemic myocardium, or whether it causes more tissue and vascular damage than that resulting from sustained coronary occlusion. Specifically, there is considerable debate regarding the role of microvascular injury that occurs as a consequence of ischemia. It is not clear whether it is a result of the necrotic process or whether it prevents reperfusion from salvaging ischemic but viable myocardial tissue, thereby increasing the extent of necrosis.

The present study was designed to characterize the spatial geometry and regional myocardial blood flow of the area of no reflow and to determine whether the no reflow phenomenon contributes to necrosis or

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is a result of the necrotic process in tissue already irreversibly injured and therefore not salvageable by any intervention including reperfusion. A secondary goal was to determine whether the no reflow phenomenon, or the development of a nonperfusable region of myocardium, is a time-limiting factor determining the extent to which reperfusion or revascularization can salvage ischemic myocardium. The answer to this question would have a profound influence on the feasibility and success of early revascularization in human beings.

Methods

Experimental preparation: Forty-one mongrel dogs of either sex weighing 20 to 34 kg were anesthetized with thiamylal sodium (30 mg/kg body weight intravenously), intubated and ventilated with a Harvard respirator delivering room air with a tidal volume of 15 ml/kg. Thoracotomy was performed through the fifth left intercostal space. After the lungs were retracted and the heart suspended in a pericardial cradle, the left anterior descending coronary artery was gently dissected free from adjacent epicardium immediately above the first diagonal branch approximately 2 cm from the origin of the left coronary artery (Fig. 1). Polyethylene catheters were placed in the left atrium for injections of dyes and radiolabeled microspheres, in the left carotid artery for measuring arterial pressure and for withdrawal of a reference blood sample during microsphere injection, and in the left jugular vein for administering intravenous injections.

The left anterior descending coronary artery was occluded with a Schwartz vascular clip above the first diagonal branch. All dogs received an intravenous bolus infusion of lidocaine, 1.5 mg/kg, immediately after coronary occlusion. Fifteen minutes after occlusion, regional myocardial blood flow was determined by injecting approximately 2.0×10^6 radioactive microspheres, 8 to 10 μ in diameter and labeled with cerium-141. After injection of the microspheres, 0.5 ml/kg of a 4 percent solution of sodium fluorescein was injected into the left atrium, and the epicardial region of low perfusion was determined using an ultraviolet light source at 340 mμ to detect fluorescent (perfused) and nonfluorescent (nonperfused) epicardium. If observed within 15 seconds of injection, the nonfluorescent region represents epicardial tissue with a regional myocardial blood flow of less than 0.4 $ml \cdot min^{-1} \cdot g^{-1}$ (Darsee JR, Kloner RA, unpublished observations). The nonfluorescent region always coincided geographically with the area of epicardial cyanosis observed with standard lighting.

Protocol: Thirty minutes after occlusion of the left anterior descending artery, the dogs were randomly assigned to one of three groups: (1) Group I (dogs subjected to 2 hours of coronary occlusion followed by 4 hours of reperfusion), (2) Group II (dogs subjected to 4 hours of coronary occlusion followed by 2 hours of reperfusion), or (3) Group III (dogs subjected to 6 hours of coronary occlusion). Dogs with an extremely small area of nonfluorescent epicardium (approximately less than 9 cm^2) resulting from extensive collateral flow from unoccluded vessels, and dogs having even one episode of ventricular fibrillation were excluded before the randomization. The fluorescein was completely washed out of the myocardial vessels within 30 minutes.

Six hours after occlusion, four dogs in each group had a second left atrial injection of microspheres labeled with tin-113 with the coronary clamp released. In the eight dogs with 2 and 4 hour occlusions, the clamp had already been released for 4 and 2 hours, respectively, to permit correlation of regional myocardial blood flow at 6 hours with the spatial geometry and transmural distribution of dyes (described later).

At the end of 6 hours, all dogs received a left atrial injection of thioflavin-S, 0.5 mg/kg, with the coronary arterial clamp released. Thioflavin-S is a fluorescent dye that stains capillary endothelium, and its absence was used to identify the area of no reflow. This injection was followed rapidly by a left atrial injection of methylene blue, 3 ml/kg, with the left anterior descending artery reoccluded to determine the in vivo area at risk for development of necrosis. We[7] have previously shown that myocardium not perfused by an in vivo left atrial injection of methylene blue has measured values for regional myocardial blood flow of less than 0.4 $ml \cdot min^{-1} \cdot g^{-1}$ tissue. Ventricular fibrillation or cardiac standstill was induced by barbiturate overdose and the hearts were excised rapidly and placed on ice.

Measurement of area of necrosis, area at risk and area of "no reflow": The right ventricle, epicardial fat and valve tissue were removed and the left ventricle was separated from the left atrium at the atrioventricular ring. The hearts were frozen rapidly in liquid Freon®, and the left ventricle was sliced into 5 mm thick transverse sections with use of a rotary blade and allowed to thaw. A clear glass plate was placed over both sides of each slice, and inner and outer margins of each slice were traced on a clear acetate sheet. With the aid of an ultraviolet light source (340 mμ), the areas not perfused by thioflavin-S after release of the coronary occlusion (area of no reflow) were traced on the same sheet. Then, the areas not perfused by methylene blue during coronary occlusion (area at risk) were also traced on the same acetate sheet. To determine the extent of myocardial cell injury, the slices were incubated in prewarmed (37° C) triphenyltetrazolium chloride (TTC) for 20 minutes as previously described.[8] Triphenyltetrazolium chloride stains normal myocardial tissue containing lactic dehydrogenase bright red; irreversibly injured tissue, depleted of lactic dehydrogenase, is not stained by TTC and remains pale yellow.

We have recently shown (Kloner RA, Darsee JR, unpublished observations) that as early as 6 hours after coronary occlusion, tissue that stains positive (red) in TTC dye is normal by ultrastructural examination except for partial depletion of glycogen, a finding to be expected after a 10 to 20 minute period of autolysis during incubation in TTC. In contrast, tissue just within the border of TTC-unstained (pale yellow) tissue showed the following ultrastructural features of irreversible ischemic myocardial cell injury: disruption of sarcomere register, profound glycogen depletion, subsarcolemmal and intermyofibrillar edema, swollen mitochondria

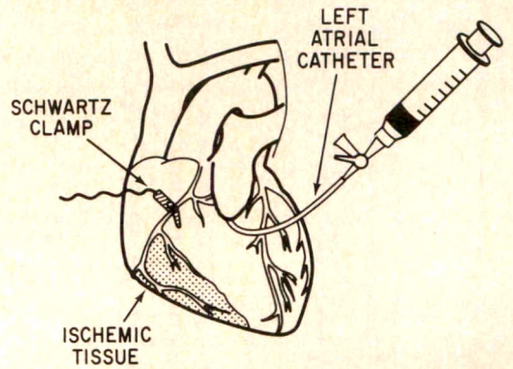


FIGURE 1. Drawing of the experimental preparation, depicting the left mid lateral region of the left ventricle. The Schwartz clamp was used to occlude the left anterior descending coronary artery and the left atrial catheter was used for injection of radioactive microspheres and dyes. The **stippled region** represents the ischemic bed.

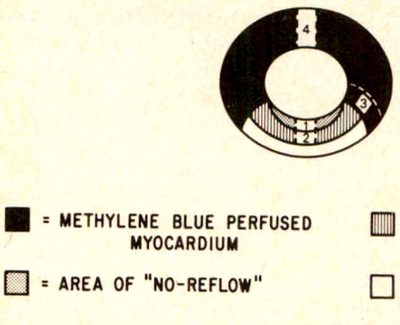


FIGURE 2. The four zones of myocardium from which tissue was dissected for analysis of regional myocardial blood flow (see text).

with disrupted cristae, and amorphous dense bodies within the mitochondria. Thus, TTC can be used to identify irreversibly injured ("infarcted") tissue as early as 6 hours after coronary occlusion, despite the absence of the usual features of necrosis on routine light microscopy. There was no evidence of partial or incomplete staining by TTC dye, and there were no zones of tissue with intermediate ultrastructural changes. Infarcted and noninfarcted areas on both sides of each slice were traced on a second clear acetate sheet.

The following values were obtained by computation using planimetric measurements: (1) the area of no reflow (A_{nr} = ratio of nonfluorescent areas to total areas of all slices); (2) the area at risk (A_r = ratio of areas not perfused by methylene blue to total areas of all slices); and (3) area of necrosis (A_n = ratio of areas not stained by TTC to total areas of all slices).

Regional myocardial blood flow: With the acetate sheet with the A_{nr} and A_r tracings placed over the TTC-stained sections as a guide, left ventricular tissue was dissected for determination of regional myocardial blood flow from the following four regions (Fig. 2): (1) area of no reflow (zone 1), (2) tissue within the area of necrosis but outside the area of no reflow (zone 2), (3) methylene blue-perfused tissue just outside the lateral border of the area at risk (zone 3), and (4) normal myocardium distant from the area at risk (zone 4). The dissected pieces of tissue were weighed (all were between 1.0 and 1.4 g), and regional myocardial blood flow and cardiac output were calculated.[9,10]

Results

Experimental groups: Of the 41 dogs, 6 were excluded because of ventricular fibrillation in the first 15 minutes after left anterior descending coronary arterial occlusion and 2 were excluded because the nonfluorescent region of epicardium after fluorescein injection was less than 9 cm^2. Of the remaining 33 dogs, 12 wer randomly assigned to Group I, 10 to Group II and 11 t Group III. None of these dogs had ventricular fibrilla tion, although several had premature ventricular com plexes and brief runs of ventricular tachycardia tha responded to administration of lidocaine. The mea body weight, total dose of anesthesia, initial and pre terminal heart rates, mean arterial pressure and tota dose of lidocaine (Group I = 120 ± 5 mg [mean ± stan dard error of the mean]; Group II = 116 ± 4 mg; Grou III = 126 ± 5 mg) did not differ statistically in the thre groups. Each dog received at least 3 mg/kg of lidocain and small supplemental doses as required. After 2 or hours of occlusion, reperfusion was not associated wit prolonged tachyarrhythmias in Group I or II, althoug several dogs had brief episodes (less than 10 seconds of ventricular tachycardia.

Myocardial fluorescence and staining: Thioflav in-S exhibited uniform fluorescence in the myocardiun (capillary endothelium) supplied by the unoccluded coronary beds and from subepicardial regions within th area at risk, but did not fluoresce from subendocardia regions within the area at risk. Methylene blue staine the myocardium transmurally in regions of the lef ventricle supplied by unoccluded coronary beds but di not stain the myocardium supplied by the occlude portion of the left anterior descending coronary artery Nonnecrotic tissue incubated in TTC stained deep red necrotic tissue appeared unstained and pale yellow.

Areas of necrosis, risk and "no reflow": The mea area at risk expressed as a percent of the left ventricl did not differ statistically (probability [p] value no significant by Student's *t* test) in Groups I (23.4 ± 3.7 percent), II (25.7 ± 2.1 percent) and III (26.9 ± 1.8 percent) (Table I). However, the three groups mani fested important differences in both the areas of n reflow (A_{nr}) and the areas of necrosis (A_n) when thes were expressed as a percent of the area at risk (A_r). Dog in Group I (2 hours of coronary occlusion, 4 hours o perfusion) had the smallest A_{nr} (11.5 ± 2.2 percent o A_r) and A_n (39.1 ± 3.2 percent of A_r). In Group II (4 hours of occlusion, 2 hours of reperfusion), A_{nr} and A_r were both larger (33.4 ± 2.8 percent and 84.5 ± 4.1 percent of the A_r, respectively; both values, $p < 0.01$ compared with values in Group I). In Group III, A_{nr} (46.7 ± 5.2 percent of A_r) and A_n (96.3 ± 1.5 percent o A_r) were even larger than in Group II (both $p < 0.01$ compared with values in Group I or II). In all dogs the

TABLE I

Relations Among Area of No Reflow, Area of Necrosis and Area At Risk Determined From Transverse Ventricular Sections

	Group I	Group II	Group III
Duration of coronary occlusion (h)	2	4	6
Duration of reperfusion (h)	4	2	0.033
Area at risk (A_r) (% total left ventricle)	23.4 ± 3.7	25.7 ± 2.1	26.9 ± 1.8
(A_n/A_r) × 100 (%)	39.1 ± 3.2*†	84.5 ± 4.1*	96.3 ± 1.5
(A_{nr}/A_n) × 100 (%)	29.4 ± 2.7*†	39.5 ± 3.6*	48.5 ± 3.8
(A_{nr}/A_r) × 100 (%)	11.5 ± 2.2*†	33.4 ± 2.8*	46.7 ± 5.2

* Statistically different ($p < 0.01$) from the mean value ± standard error of the mean in Group III by Student's *t* test. † $p < 0.01$ compared with Group II; all values for areas are mean ± standard error of the mean.

A_n = area of necrosis; A_{nr} = area of "no reflow"; A_r = area at risk.

area of no reflow was contained topographically within necrotic tissue, was always smaller than the area of necrosis and occupied its subendocardial portion (Fig. 3 and 4).

Regional myocardial blood flow: The results of measurements obtained 15 minutes after occlusion (Table II) showed no significant group differences among mean flow values in either ischemic or nonischemic tissue. Furthermore, the comparison of flow values during reperfusion measured 6 hours after occlusion with values measured 15 minutes after occlusion showed no significant increase in regional myocardial blood flow within the area of no reflow (zone 1) even with 4 hours of reperfusion. However, the necrotic tissue just outside the border of the area of no reflow (zone 2) in Groups I and II showed a rise in regional myocardial blood flow after reperfusion to at least 71 percent of values in normal tissue, even though this tissue remained necrotic (Fig. 5). Although this improvement in regional myocardial blood flow was not as striking in necrotic tissue in Group III, there was an increase over values obtained 15 minutes after occlusion.

Discussion

Four conclusions can be drawn from this study: (1) The area of no reflow during reperfusion is smaller than,

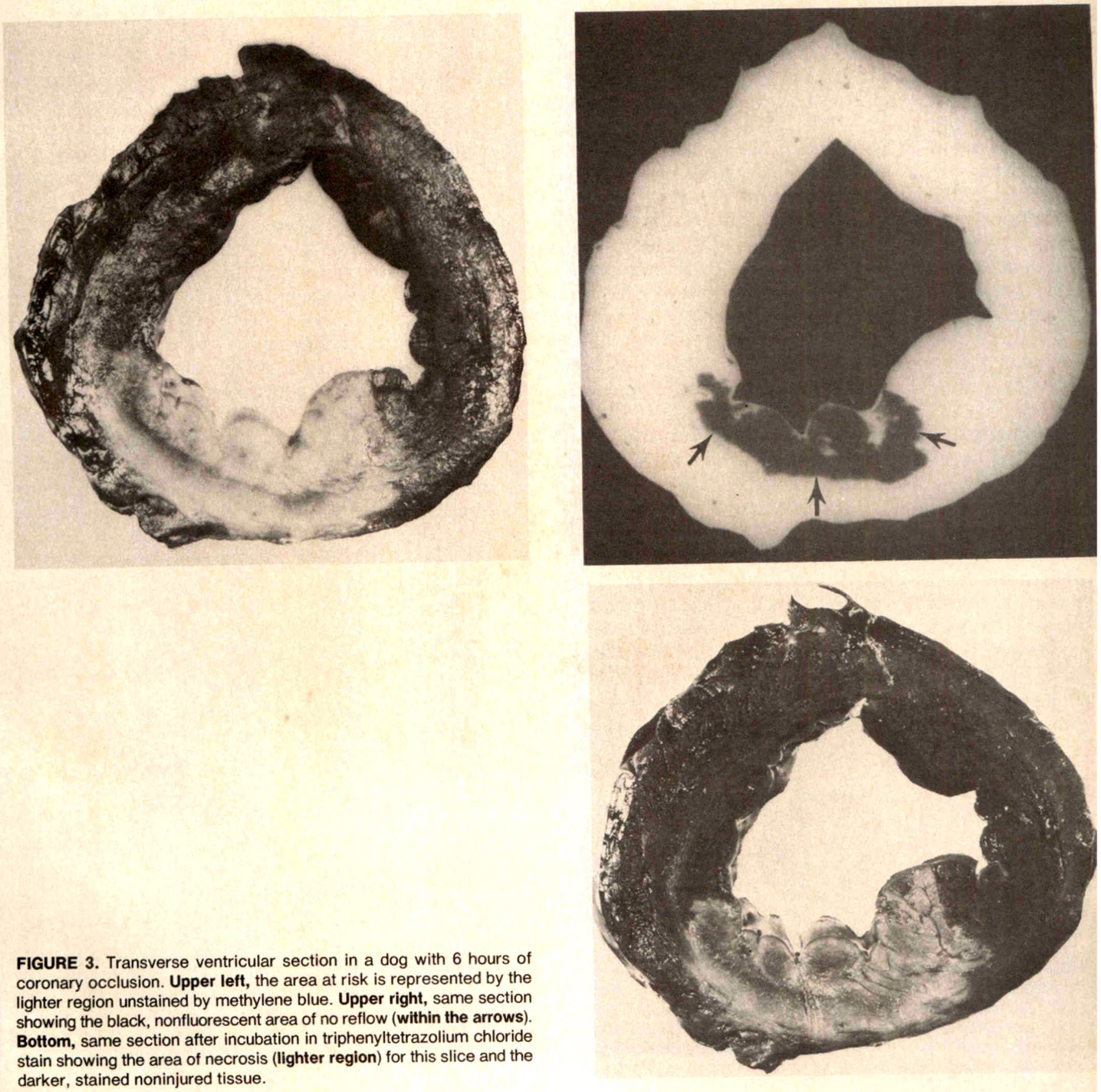


FIGURE 3. Transverse ventricular section in a dog with 6 hours of coronary occlusion. **Upper left,** the area at risk is represented by the lighter region unstained by methylene blue. **Upper right,** same section showing the black, nonfluorescent area of no reflow (**within the arrows**). **Bottom,** same section after incubation in triphenyltetrazolium chloride stain showing the area of necrosis (**lighter region**) for this slice and the darker, stained noninjured tissue.

TABLE II

Regional Myocardial Blood Flow (RMBF) Immediately After Left Anterior Descending (LAD) Coronary Occlusion and at 6 Hours After Release of Occlusion

RMBF	Group I	Group II	Group III
15 minutes after LAD occlusion ($ml \cdot min^{-1} \cdot g^{-1}$; n = 33)			
Zone 1	0.11 ± 0.01	0.15 ± 0.02	0.19 ± 0.02
Zone 2	0.20 ± 0.02	0.24 ± 0.01	0.26 ± 0.03
Zone 3	0.61 ± 0.01	0.58 ± 0.03	0.56 ± 0.02
Zone 4	1.05 ± 0.02	1.02 ± 0.03	1.04 ± 0.02
6 hours after release of LAD occlusion ($ml \cdot min^{-1} \cdot g^{-1}$; n = 12)			
Zone 1	0.10 ± 0.01	0.13 ± 0.03	0.18 ± 0.02
Zone 2	0.78 ± 0.05*	0.71 ± 0.04*	0.45 ± 0.03†
Zone 3	1.00 ± 0.03*	0.94 ± 0.05*	0.91 ± 0.07*
Zone 4	1.07 ± 0.04	1.01 ± 0.05	1.09 ± 0.04

* Statistically different from values for regional myocardial blood flow 15 minutes after coronary occlusion ($p < 0.01$; Student's *t* test for paired comparison). † $p < 0.05$.

Zones 1, 2, 3 and 4 are as depicted in Figure 1.

and contained within, the borders of the area of necrosis; (2) the area of no reflow is not a time-limiting factor determining the extent to which reperfusion or revascularization can salvage ischemic myocardium because it is surrounded by tissue that is necrotic; (3) although regional myocardial blood flow does not increase during reperfusion in necrotic tissue within the area of no reflow, improvement in flow does occur in surrounding necrotic tissue, thus suggesting that the microvasculature in this region remains intact; and (4) reperfusion does not appear to increase the quantity of ischemic tissue that becomes necrotic because coronary occlusions of briefer duration followed by reperfusion resulted in substantially less necrosis after 6 hours than did longer occlusions with briefer periods of reperfusion.

Efficacy of reperfusion in preserving ischemic myocardium: There are many methods of protecting ischemic myocardium from necrosis in animals during experimental coronary occlusion or in patients with acute myocardial infarction.[2,11–13] The most direct experimental approach to the preservation of myocardial cells has been to increase the supply of oxygen and metabolic substrates by restoring or at least improving blood flow to the occluded vascular bed. However, conflicting results regarding the efficacy of reperfusion have been reported. Maroko et al.[14] showed that after 3 hours of coronary occlusion in anesthetized dogs, reperfusion was accompanied by significantly less depression of myocardial creatine kinase activity and histologic necrosis than those found in dogs with permanent occlusion. Reimer et al.[15] also showed that reperfusion after 40 minutes to 6 hours of coronary occlusion resulted in significantly smaller myocardial infarcts than those found with permanent coronary occlusions of 2 to 4 days' duration. Constantini et al.[16] reported that, in dogs subjected to permanent coronary occlusion for 7 days, ventricular function remained depressed throughout the 7 day period and infarcted area averaged 32 percent of the left ventricle. In dogs with 3 hours of coronary occlusion followed by 7 days of reperfusion, ventricular function gradually returned to preocclusion values and the infarcted area was only 14 percent of the left ventricle.

Not all studies have shown that reperfusion is beneficial. For example, in intact conscious dogs Mathur et al.[17] produced coronary occlusion that was either permanent for 7 days or of 2 or 5 hours' duration and followed by reperfusion for 7 days. They found that the dogs with reperfusion were more likely to have arrhythmias, earlier development of electrocardiographic Q waves and accelerated hemodynamic deterioration in the postreperfusion period. In another study[18] re-



FIGURE 4. Representative drawings of the topographic relations among the area of no reflow (**stippled region**), the area of necrosis (**hatched region plus the stippled region**) and the ischemic area at risk (**white region plus the area of necrosis**) for the three groups of dogs. The area of no-reflow was always smaller than, and contained within, the area of necrosis.

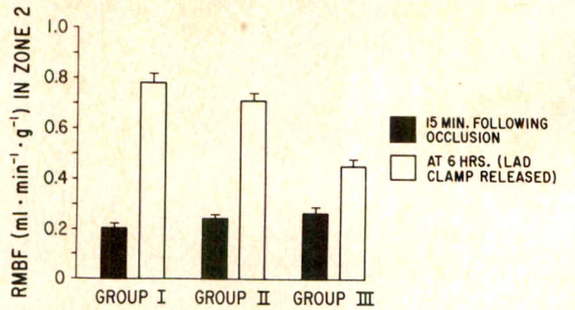


FIGURE 5. Comparison of values for regional myocardial blood flow (RMBF) 15 minutes after occlusion with values obtained after 6 hours with the left anterior descending (LAD) coronary arterial clamp removed. In all three groups of dogs, the increase in regional myocardial blood flow in zone 2 was significantly greater at 6 hours even though the tissue was necrotic.

perfusion after 3 hours of coronary occlusion in the pig resulted in extensive intramyocardial hemorrhage and no evidence of improvement in myocardial function. Hemorrhagic areas in the heart were found at necropsy in patients who underwent coronary bypass surgery in the first 7 days after myocardial infarction.[19] Ultrastructural evidence of apparent acceleration of necrosis and explosive cell swelling were described in severely ischemic tissue after reperfusion[20]; however, because this phenomenon occurred only in irreversibly injured tissue its significance is uncertain. Reperfusion did not seem to enlarge the area of necrosis, but only accelerated the process within a given quantity of irreversibly injured tissue.

The area of no reflow: One factor influencing the effects of reperfusion was not examined in these previous studies: the no reflow phenomenon, which was observed in the anesthetized dog with a temporary occlusion of the left circumflex coronary artery.[6] After 40 minutes of ischemia plus arterial reperfusion, injected fluorescent dyes were evenly distributed throughout the damaged tissue. In contrast, when reflow was allowed after 90 minutes of ischemia, portions of the inner subendocardial half of damaged myocardium (in the posterior papillary muscle) were not perfused by the dyes. Electron microscopy of this poorly perfused tissue showed severe capillary damage, decreased numbers of pinocytic vesicles, intraluminal fibrin thrombi and extravascular fibrin deposits and erythrocytes. Myocardial cells were swollen in both poorly perfused and well perfused irreversibly injured tissue. Contraction bands and intramitochondrial calcium accumulation were prominent features of irreversible injury with reflow at 40 minutes but were not noted after 90 minutes of ischemic injury in regions with poor perfusion. However, the exact spatial relations among the area of no reflow, the area of necrosis, and the area of potentially salvageable myocardium within the ischemic area at risk were not determined in the previous study. In the present study, the area of no reflow was always subendocardial and confined well within the limits of myocardial cell necrosis as determined by the TTC technique. Portions of the outer myocardial wall within the area at risk received significant reflow that resulted in subepicardial myocardial salvage.

Reperfusion and role of microvascular damage: Although the results of experimental studies of the efficacy of reperfusion have been contradictory, the quantity of tissue salvageable by reperfusion appears to be determined primarily by the length of occlusion and is not influenced by the presence of tissue that is no longer perfusable. This conclusion is consistent with other observations in our laboratory[21] showing that in dogs subjected to coronary occlusions of only 20 minutes' duration, ultrastructural evidence of myocardial cell injury preceded evidence of microvascular damage. Both myocardial cell injury and microvascular damage progressed between 40 and 90 minutes of occlusion, but microvascular damage remained confined within areas that already showed severe myocardial cell injury, thus suggesting that microvascular damage was not a primary cause of myocardial cell injury. In a study of closed chest dogs subjected to 5.5 hours of coronary occlusion and 30 minutes of reperfusion, Fishbein et al.[22] found that the extent of hemorrhage and vascular injury evaluated histologically was less than the extent of myocardial infarction evaluated with both triphenyltetrazolium chloride-staining and histologic study, and was contained within the central and subendocardial portions of the infarcted tissue. They concluded that reperfusion hemorrhage occurs only within infarcted tissue manifesting severe vascular injury before reperfusion and that hemorrhage with reperfusion does not increase myocardial infarct size.

Clinical implications: Whether the no reflow phenomenon occurs in human patients has not yet been determined. With the current interest in the use of pharmacologic agents that increase blood flow to the ischemic bed, and in the light of recent reports of successful and beneficial early revascularization,[23] the presence of a no reflow phenomenon in human subjects could have important clinical implications. Damaged tissue that cannot be reperfused would be uninfluenced by any form of drug therapy or by flow provided by coronary bypass grafting. However, because this nonreperfusable region appears to occupy a portion of a larger surrounding necrotic zone, its effects on the salvageability of surrounding tissue are probably negligible. The perfusable part of the necrotic zone is also not likely to be influenced by interventions, although its rate of healing may be affected. The ischemic tissue outside the area of necrosis is the region of myocardium on which coronary vasodilators, early revascularization surgery and other preservation efforts will have their most profound influence. The ability to preserve ischemic myocardium depends on the efficacy of the individual agent, the time of its administration and the quantity of ischemic but still viable tissue. The latter is influenced primarily by the duration of the period between the onset of ischemia and the time of the intervention, and not by the existence, distribution or spatial geometry of the no reflow phenomenon.

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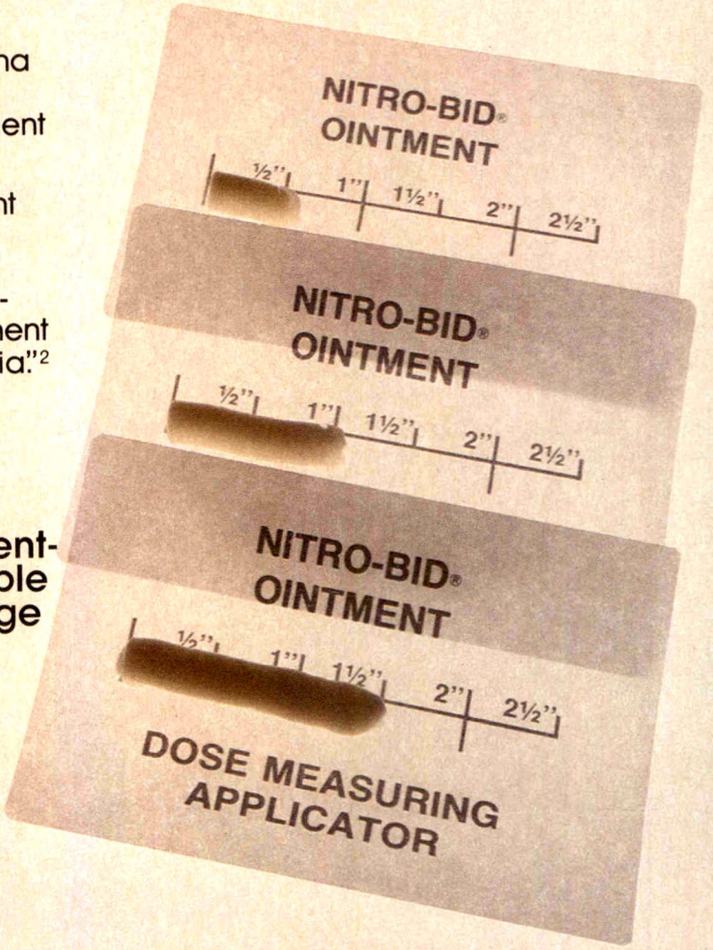
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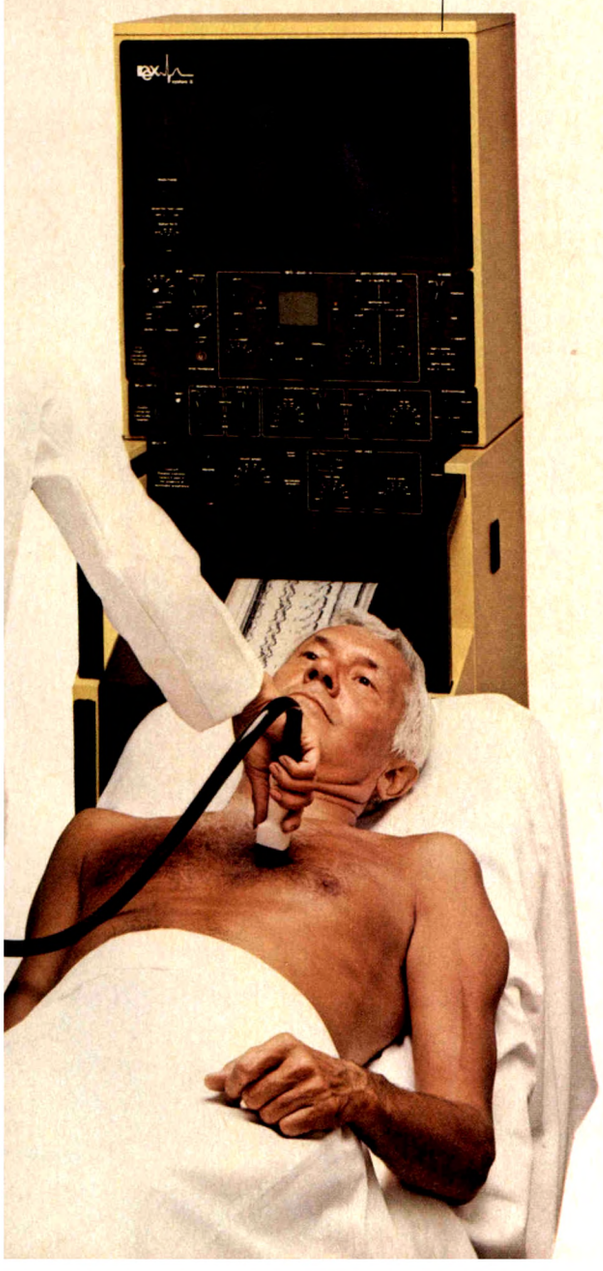
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CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

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Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE Usual dietary intake potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

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HOW SUPPLIED Bottles of 100.

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CONTRAINDICATIONS

Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS

Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS

Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION

One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

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Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.

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N 0071-0569-13—Convenience Package.

0.4 mg (1/150 grain): N 0071-0570-24 [06]—bottle of 100 tablets;
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0.6 mg (1/100 grain): N 0071-0571-24 [06]—bottle of 100 tablets;
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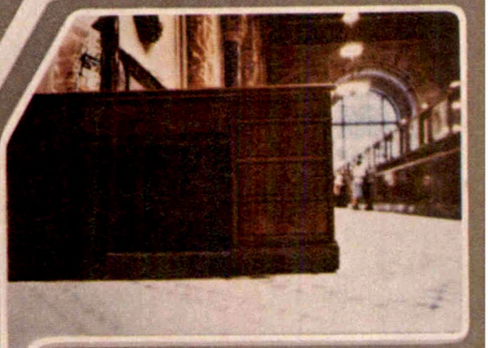
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(nitroglycerin tablets, USP) 4×25s

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For brief summary of the prescribing information, please see the preceding page.

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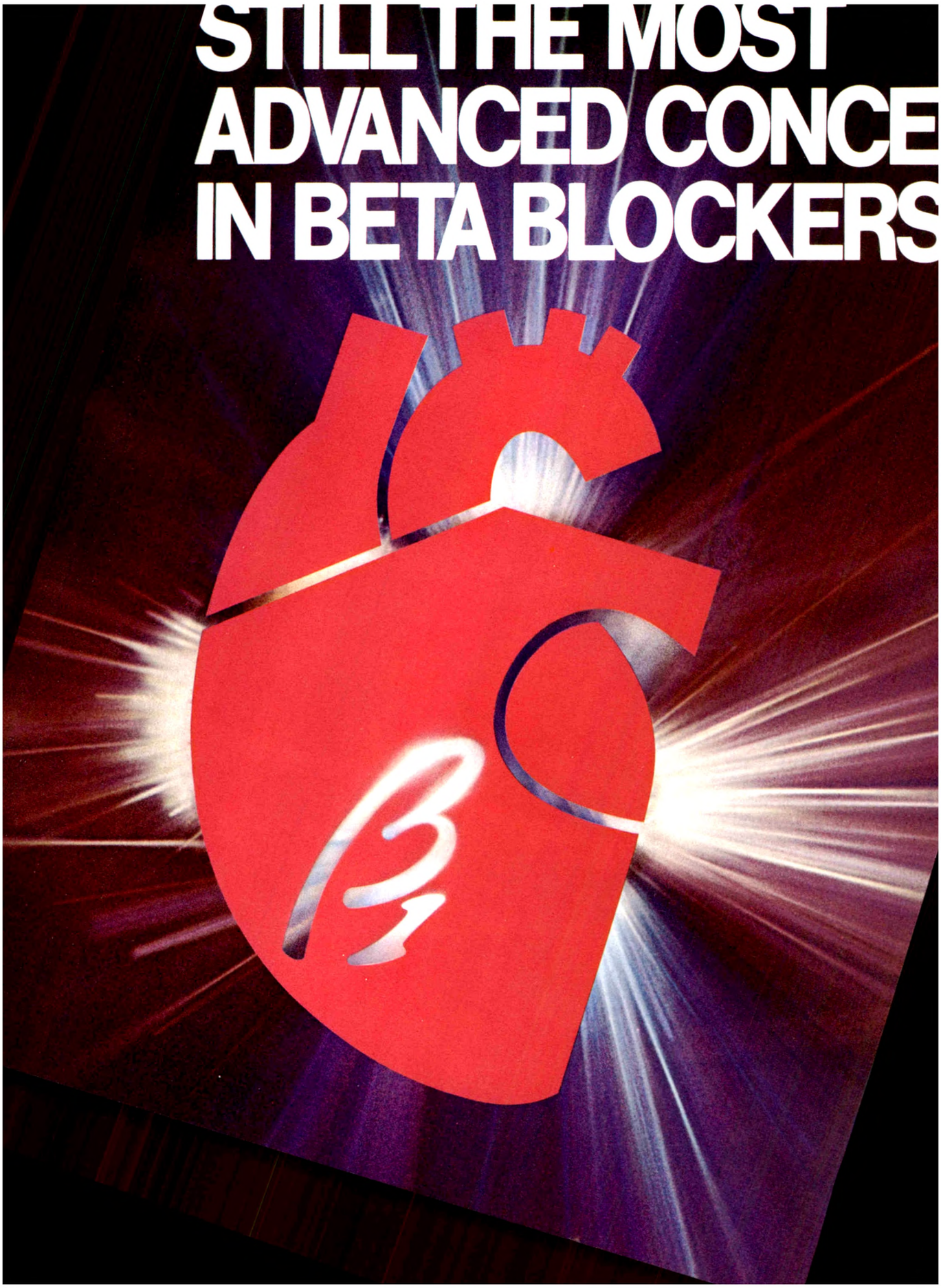
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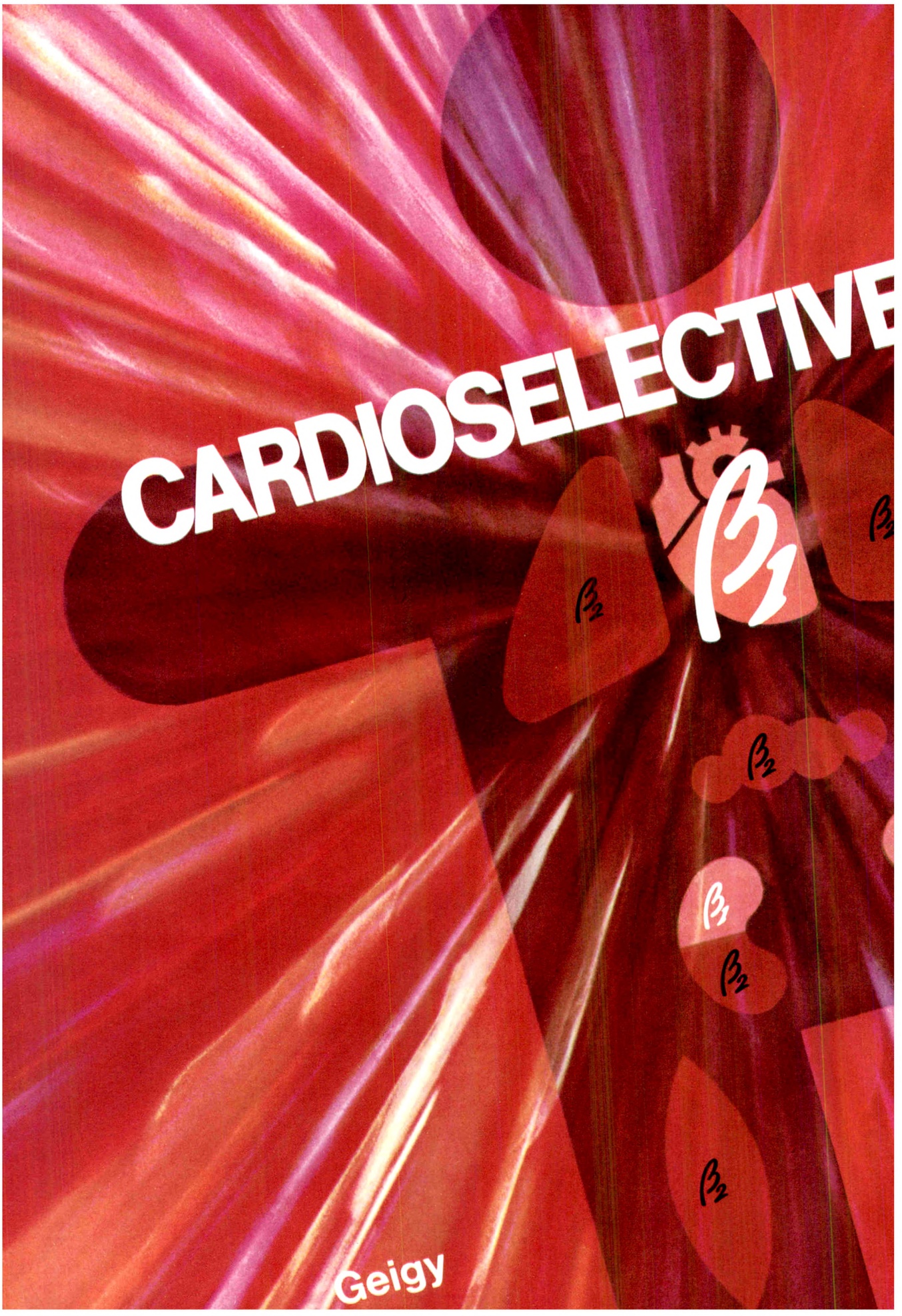
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exerts a relative preference for beta-one receptors.

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By concentrating its action on the beta-one receptors involved in blood pressure control and to a large extent—at usual therapeutic dosages—avoiding the unwanted effects of beta-two blockade, Lopressor offers potential benefits not available with the nonselective beta blockers.

PHARMACOLOGICAL EVIDENCE FOR SELECTIVITY…

LESS EFFECT ON PERIPHERAL CIRCULATION AFTER EXERCISE[1]
Propranolol, due to beta-two blockade, causes a greater reduction in muscle blood flow than does Lopressor.

REDUCES THE PRESSOR EFFECT OF EPINEPHRINE[2]
Propranolol augments the pressor effect of epinephrine, while Lopressor reduces the pressor effect.

BETTER TOLERABILITY IN PATIENTS WITH ASTHMA[3]
At an antihypertensive dosage (100 mg daily) there was no difference in FEV, and no patients reported any influence on their asthma.

Lopressor should be used with caution in patients with bronchospastic disease. Since beta-one selectivity is not absolute, bronchospastic patients should receive a beta-two-stimulating agent concomitantly. For complete details, see the Warnings section of the prescribing information.

Please see next page for brief summary of prescribing information.

B2

Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 1 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1/100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

667292 C79-22 (8.7

For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

References

1. McSorley PD, Warren DJ. Effects of propranolol and metoprolol on the peripheral circulation. *Br Med J* 1978 (Dec. 9), **2**:1598-1600.
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Methodologic Problems of Exercise Testing for Coronary Artery Disease: Groups, Analysis and Bias

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New Haven, Connecticut

To determine why exercise testing remains controversial as a diagnostic test for coronary artery disease, a methodologic review was undertaken of 33 studies comprising 7,501 patients who had undergone both exercise tests and coronary angiography. Of seven methodologic standards for research design, only one received general compliance: the requirement for an adequate variety of anatomic lesions. Less than half of the studies complied with any of the remaining six standards: adequate identification of the groups selected for study; adequate analysis for relevant chest pain syndromes; avoidance of a limited challenge group; and avoidance of work-up bias, diagnostic review bias and test review bias. Only one study met as many as five standards.

These methodologic problems may explain the wide range of sensitivity (35 to 88 percent) and specificity (41 to 100 percent) found for exercise testing, because the variations could not be attributed to the usual explanations: definition of anatomic abnormality, stress test technique or definition of an abnormal test. Determining the true value of exercise testing requires methodologic improvements in patient selection, data collection and data analysis.

For more than 40 years exercise testing has been used as a diagnostic test for coronary disease. The popularity of the test has recently increased because of several advances. First, it is now recognized that exercise testing, when carefully monitored, can be safely performed even in patients with advanced coronary disease. Second, new techniques apparently offer significant advantages over the Master two-step test. Third, exercise testing equipment has been marketed for installation in many physicians' offices, thus making it readily available to patients. Despite the extensive clinical and research experience that has followed these advances, the value of the test remains controversial. We undertook this review to determine why.

Methods

Studies analyzed: To investigate the controversy we identified the studies published in English between January 1967 and August 1979 that included at least 50 patients who had had an exercise test as well as a coronary angiogram that had been used to define the presence of coronary artery disease. The 33 studies[1–33] that met these specifications are the basis for this review.

Measures of test efficacy: To compare the results of the studies, we used quantitative indexes of "efficacy" that are usually calculated as shown in Table I. The most useful measures of efficacy are "positive predictive accuracy" and "negative predictive accuracy," defined as $a/(a + b)$ and $d/(c + d)$, respectively. These indexes allow a clinician, given the result of a test, to predict the likelihood of the patient's having the specified disease. Unfortunately, these indexes of "accuracy" vary with the prevalence of the disease, resulting in different values for different tested populations. To avoid this problem of a prevalence-dependent index, efficacy is usually measured by "sensitivity" and "specificity," defined as $a/(a + c)$ and $d/(b + d)$, respectively. These indexes are less useful clinically than the indexes of "accuracy," because they show the chance of a given

From the Robert Wood Johnson Clinical Scholars Program and the Departments of Medicine and Epidemiology, Yale University School of Medicine, New Haven, Connecticut. This work has been supported in part by the Veterans Administration. Manuscript received March 10, 1980; revised manuscript received June 10, 1980, accepted June 13, 1980.

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TABLE I

Data for Calculating Indexes of Efficacy

Test Result (exercise test)	Confirmed Disease State (positive angiogram)	
	Present	Absent
Positive	a	b
Negative	c	d

test result after the presence or absence of the disease has been determined. However, because the sensitivity and specificity indexes are not dependent on disease prevalence,[34] we used them for comparing results.

Results

Reasons for Wide Variations in Accuracy

The 33 individual studies had wide variations in sensitivity (35 to 88 percent) and specificity (41 to 100 percent) (Table II). The sensitivity levels of the studies were spread throughout the range of values; and the specificity levels, although somewhat clustered around higher values, also had a wide range. Three explanations are frequently offered for such wide variations: (1) differences in criteria defining the disease; (2) differences in methods or protocols for test performance; and (3) differences in the definition of an abnormal test. When we examined each of these possible explanations, the following results were noted:

1. Differences in criteria defining coronary artery disease: The criteria for angiographic diagnosis in the reviewed studies were almost evenly split between two definitions of coronary artery disease: 50 percent versus 70 to 75 percent narrowing of luminal diameter. Table III shows the variation in sensitivity and specificity of the studies according to these two definitions of coronary disease. If the variations were largely due to differences in definition of disease, the diagnostic separation should reduce the spread of sensitivity and specificity in the subgroups. However, as Table III shows, wide variability remains regardless of which definition is used for coronary disease.

2. Differences in stress test protocols: These differences, by causing differences in performance of the test, might also cause variation in test results. Seven studies used a Master or double Master test; 19 used a graded treadmill or bicycle test aiming for an end point heart rate of 85 to 90 percent of a predicted maximal rate; 7 used a graded treadmill or bicycle test aiming for an unspecified "maximal" rate. Separation of results according to these three protocols (Table IV) does not reduce the variations in sensitivity and specificity. An additional aspect of the test protocol is the use of different electrocardiographic lead systems, which have also been shown to cause variability in stress test results.[29,35] However, the variability in sensitivity and specificity of the 33 studies was unaffected by the number of leads—0, 1 to 4, or 5 to 12—monitored during the test.

3. Differences in the definition of an abnormal stress test: This commonly offered cause of variation is receiving major attention in current research on exercise testing. Of the multiple definitions of an abnormal exercise test used in the 33 studies, only S-T segment depression was used frequently enough to be compared. This widely used electrocardiographic indication of ischemia was generally specified as being flat or downsloping for at least 0.08 second. Almost all studies could be compared according to one or more degrees of S-T segment change. Table V shows that the wide variation persisted across all but one definition of an abnormal test. The little variation in specificity of a 2 mm S-T change was offset by a wide range of very low sensitivities.

Methodologic Standards in Testing for Coronary Disease

Because the customary explanations did not account for the observed variations, we looked for alternative possibilities. One of the most prominent seemed to be basic differences in research design, an approach that had been useful in explaining conflicts in studies of anticoagulant therapy for acute myocardial infarction.[36] Because this review deals with a diagnostic test rather than a therapeutic regimen, new standards for research design had to be proposed. Beginning with Ransohoff and Feinstein's discussion[37] of problems in evaluating the efficacy of diagnostic tests, we developed seven

TABLE II

Variation in Sensitivity and Specificity in 33 Studies

Values of Sensitivity or Specificity (%)	Sensitivity (number of studies)	Specificity (number of studies)
31–40	2	0
41–50	4	2
51–60	6	0
61–70	6	3
71–80	5	5
81–90	9	11
91–100	1	12

TABLE III

Differences in Angiographic Definition of Coronary Artery Disease (50 or 75 percent reduction [R] in luminal diameter) in 31 Studies*

Values of Sensitivity or Specificity (%)	Sensitivity (number of studies)		Specificity (number of studies)	
	50% R	75% R	50% R	75% R
31–40	2	0	0	0
41–50	3	0	2	0
51–60	3	3	0	0
61–70	4	2	1	2
71–80	3	1	1	3
81–90	2	7	6	4
91–100	0	1	7	5
Total	17	14	17	14

* Two studies did not supply specific angiographic criteria.

TABLE IV

Differences in Stress Test Protocol in 33 Studies

Values of Sensitivity or Specificity (%)	Sensitivity (number of studies)			Specificity (number of studies)		
	Master 2 Step	Graded (85–90% maximal)	Graded ("maximal")	Master 2 Step	Graded (85–90% maximal)	Graded ("maximal")
31–40	1	1	0	0	0	0
41–50	2	2	0	1	1	0
51–60	1	3	2	0	0	0
61–70	2	3	1	0	2	1
71–80	0	5	0	2	3	0
81–90	1	4	4	2	5	4
91–100	0	1	0	2	8	2
Total	7	19	7	7	19	7

methodologic standards addressing important issues in diagnostic test research. These standards, concerned with the selection of study groups, the analysis of data and the avoidance of potential sources of bias, were then applied to each of the 33 studies. We hoped to find a reduction in variability of results in the studies that seemed most effectively planned.

Table VI lists each study under review, the number of patients in the study, the results for sensitivity and specificity, the stress test protocol used and the angiographic criterion for coronary artery disease, together with a listing of the standards that each study satisfied. Details of the standards and associated scores are listed in the sections that follow. Because the scoring was based on the published text of each study, some ratings might have been changed if the pertinent information had been reported by the study authors. Because problems in any one of these standards could produce inaccurate results for a study, no attempt was made to create an overall score. The content and ratings for each standard were as follows:

Standard 1: adequate identification of the groups selected for study: Patients undergoing stress testing and coronary angiography are a highly selected group. However, the clinical criteria justifying angiography vary among individual physicians and institutions, leading to differences in groups being studied. In addition, investigators may use different criteria for admitting patients into a study, even after angiography has been performed. Thus, groups selected for study may vary widely, from asymptomatic air force pilots to elderly men with typical angina pectoris. To encourage adequate study group identification, this standard required that the method of selecting patients be described *and* that the demographic and clinical characteristics of the study group be reported. The first part of this standard was satisfied by a statement of eligibility criteria clear enough to allow the same group of patients to be selected if the study were repeated. A study group of "680 consecutive patients undergoing an exercise test and angiogram,"[29] or of the "302 patients who underwent both an exercise test and angiogram . . . in the last four years"[28] would fulfill this part of the standard; but a group "referred for diagnostic evaluation"[21] or "selected on clinical grounds"[25] would not satisfy the standard. The second part of the standard required a summary statement of the patients studied in relation to age, sex and symptoms of coronary disease or reason for angiography. Only 16 studies (48 percent of the 33) met both parts of this standard.

Standard 2: adequate analysis of anatomic lesions: This standard, concerned with the analysis of anatomic lesions, was intended to allow evaluation of the test over the full anatomic spectrum of coronary artery disease. For example, it is important to know if the sensitivity and specificity of left main coronary ar-

TABLE V

Differences in Definition of an Abnormal Stress Test (degree of S-T segment depression [↓]) in 32 Studies*

Values of Sensitivity or Specificity (%)	Sensitivity			Specificity		
	≥0.5 mm ↓	≥1 mm↓	≥2 mm ↓	≥0.5 mm ↓	≥1 mm ↓	≥2 mm ↓
11–20	0	0	2	0	0	0
21–30	0	0	3	0	0	0
31–40	1	2	2	0	0	0
41–50	1	2	1	0	2	0
51–60	3	5	0	1	0	0
61–70	0	6	1	1	3	0
71–80	0	5	0	3	4	0
81–90	3	8	0	3	9	1
91–100	0	1	0	0	11	8
Total	8	29	9	8	29	9

* When data were available, a study was counted in more than one category. One study did not supply S-T segment data.

TABLE VI

Summary of Studies and Results of Methodologic Review

Ref	Year	Cases (n)	Sensitivity (%)	Specificity (%)	Test Protocol*	Definition of Disease†	Specific Standards Satisfied‡
1	1967	55	66	100	M,DM	50	2, 3, 4
2	1967	65	84	81	B	§	1, 3, 6
3	1967	75	64	49	DM	50	2, 3, 4
4	1967	84	78	89	B, T	50	1, 2, 3, 7
5	1968	68	47	97	B	50	2, 3, 4
6	1970	100	73	82	T	50	1, 4
7	1970	52	57	81	DM	50	
8	1971	160	48	80	DM	§	1, 2
9	1971	110	86	73	DM	75	2
10	1971	100	35	100	M	50	1, 2, 3, 6, 7
11	1971	96	59	94	B	50	1
12	1972	100	62	89	T	50	1, 2, 7
13	1972	166	81	95	T	75	2, 7
14	1973	74	54	96	T	75	1, 7
15	1974	465	65	92	T	70	1, 2, 3
16	1974	70	65	83	B	75	3, 6
17	1974	50	83	89	T	75	2, 4, 5, 7
18	1975	251	53	88	T	75	2
19	1975	89	49	41	B	50	1, 2, 3
20	1976	153	45	89	DM	75	2
21	1976	283	73	78	T	50	2, 7
22	1977	98	55	85	T	50	1, 2, 6, 7
23	1977	278	86	70	B	50	2, 3, 7
24	1978	100	88	82	T	70	1, 2, 6, 7
25	1978	1222	53	91	T	75	2, 4
26	1978	70	81	100	T	50	2, 4, 7
27	1978	164	84	67	T	70	2
28	1978	302	76	76	B, T	70	5
29	1979	200	84	72	T	70	1, 2, 3, 6
30	1979	2045	79	69	T	70	1, 2, 3
31	1979	181	40	92	B	50	1, 3, 4, 7
32	1979	100	91	96	B	75	2, 3, 6, 7
33	1979	75	63	95	B	50	1, 2, 7

* B = bicycle; DM = double Master; M = Master; T = treadmill. † Expressed as percent luminal narrowing on coronary angiogram. ‡ See text for description of the seven standards under review. § Disease defined by an index of severity rather than percent luminal narrowing.

tery disease are different from those of single vessel disease. Twenty-five studies (75 percent) met this standard by reporting the number or location of involved vessels (for example, two vessel or left main coronary artery disease) and by citing the stress test results for each anatomic subgroup. For example, Goldschlager et al.[21] satisfied the standard by providing the sensitivity and specificity of stress testing in patients with one, two and three vessel disease together with the number of patients in each anatomic subgroup.

Standard 3: adequate analysis for relevant chest pain syndromes: Because the spectrum of clinical syndromes as well as the anatomic spectrum of coronary disease should be considered, this standard was intended to ensure that the stress test was examined in patients with the common chest pain syndromes that usually lead to performance of the test. For example, does the test have the same sensitivity and specificity for typical angina pectoris as for "atypical" chest pain? This standard, met by only 14 studies (42 percent), required the report of sensitivity and specificity for at least one such clinical syndrome. An example of failure to meet this standard occurred in a study[24] in which the authors reported the number of patients with various chest pain syndromes, but did not analyze the exercise results separately for these subgroups. However, in a later paper,[29] the same authors satisfied the standard by analyzing their results according to the categories of "non-specific" chest pain, "probable angina" and "typical angina."

Standard 4: avoidance of a limited challenge group: This standard was designed to prevent excessively limiting the study group by excluding patients with clinical conditions that might cause false negative or false positive results. When such exclusions occur, the test can be applied with confidence only to a narrow clinical spectrum that frequently does not include the patients for whom the test is most often ordered or needed.[37] For example, the stress test would be very useful if it could distinguish between chest pain associated with mitral valve prolapse and coronary artery disease. However, if patients with mitral valve prolapse have routinely been excluded from exercise studies because of fears of false positive results, their stress test results are unknown. Similarly, patients with suspected coronary disease will often be taking antianginal drugs. It would appear desirable to include such patients in an exercise study to determine whether the sensitivity and specificity of their test differs from those of other groups. By studying the full spectrum of patients who are eligible for an exercise test, and by analyzing subgroups of patients believed to have high rates of false positive and false negative tests, a clearer understanding of the test's clinical usefulness will emerge.

Standard 4 was met if no exclusions were made that would reduce the chance of a false positive result (for example, therapy with digoxin, aortic stenosis or abnormal S-T segment) or a false negative result (for example, therapy with beta adrenergic blocking agents). Only eight studies (24 percent) met this standard (Table VI). Only three studies (9 percent) analyzed such a condition separately to determine the usefulness of the test in that clinical subgroup.

Standard 5: avoidance of work-up bias: Work-up bias occurs when the results of the exercise test influence a patient's chance to be entered into a study.[37] For example, when the exercise test is positive rather than negative, a patient may be more likely to undergo the expense and discomfort of coronary angiography. Consequently, a disproportionate number of people with a positive stress test may be entered in the study. This bias would be likely to increase the relative number of those with a positive exercise test (a and b in Table I) and would result in falsely high sensitivity and falsely low specificity levels.

Only two studies (6 percent) met standard 5. The requirement for avoiding this bias was a study design that either enrolled patients before the stress test was performed or used a special strategy to measure or limit work-up bias (for example, asking physicians how the stress test result affected their decision to perform the coronary angiogram). The standard was met by Weiner et al.,[28] who stated that "in each case the decision to do angiography was made prior to the exercise test." In most other studies, the standard was not met because the patients were selected from the list of those having coronary angiography.

Standard 6: avoidance of diagnostic review bias: This standard required the avoidance of the diagnostic review bias that can occur when the result of the stress test is allowed to influence the interpretation of the coronary angiogram. This bias, as well as the test review bias (see later), would be likely to encourage concordance between the exercise test and the angiogram, resulting in a relative increase in a and d (Table I) that would falsely improve both sensitivity and specificity. Only seven studies (21 percent) met this standard, which required a statement that the interpreters of the angiogram did not know the stress test result. The use of several independent readers would not fulfill the standard if they were aware of the stress test result.

Standard 7: avoidance of test review bias: Standard 7 is analogous to standard 6. Test review bias occurs when the result of the coronary angiogram is allowed to influence the interpretation of the stress test. This standard, met by only 14 studies (42 percent), required a statement that the exercise test was interpreted without knowledge of the angiographic findings. Four studies met both the test review and diagnostic review bias standards. No study met all three standards dealing with bias.

In summary, there was general compliance with only one standard: adequate analysis of anatomic lesions. Only one study met as many as five standards; eight met as many as four. All studies failed two or more standards.

Discussion

The controversy about exercise testing in the diagnosis of coronary disease is justified by the wide variation in the results of the reviewed studies. The variation is commonly attributed to differences in performance of the test, in criteria for an abnormal result and in angiographic definition of coronary artery disease. However, the results of our analysis suggest that a principal source of the variation may be methodologic defects in research design. When we considered seven methodologic standards intended to provide complete, unbiased evaluations of the test, we found that each study failed to adhere to at least two of the standards. These variations in methodology alone could readily produce inaccurate and highly variable results.

Most new work on the exercise test in diagnosis has concentrated on developing better test procedures, such as the exercise thallium study,[38] and better identification of an abnormal test, such as multifactorial criteria that improve on the use of the S-T segments alone.[27] Without simultaneous improvements in the basic design of the studies, the true efficacy of these new techniques may never be established.

Recommendations for improved study design: Because the cited methodologic standards can be fulfilled with a wide variety of research strategies, we are reluctant to prescribe rigid instructions for the performance of studies evaluating diagnostic efficacy. Nevertheless, certain general principles can be stated.

In assembling the study groups, the investigator should establish unambiguous admission criteria that give all of the eligible patients an equal chance to be included. Whenever possible, patients should be included who are suspected to have an increased rate of false positive and negative test results. These patients can be analyzed separately in relevant subgroups as described earlier.

To avoid bias in the collection of data, two independent readers should interpret the coronary angiograms without knowledge of the clinical and stress test findings. Similarly, two independent readers should interpret the stress test without knowledge of the angiographic results. To measure the potential impact of work-up bias, the results of the study should be analyzed separately for those patients whose decision to undergo angiography was not related to the results of the exercise test.

Finally, the data should be separated according to relevant anatomic and clinical subsets. The anatomic subsets might include the number and severity of coronary lesions and certain recognizable high risk abnormalities. Clinical subsets might be selected according to the symptoms leading to ordering the test (for example, chest pain or breathlessness), characteristics of the symptoms (for example, typical versus atypical angina) or certain associated diseases (hypertension, valvular heart disease or congestive heart failure).

Even with improvements in the basic design of the research, the sensitivity and specificity of exercise testing may remain highly variable. The arteriogram measures anatomic abnormalities, but the exercise test measures the heart's physiologic response to increased

work. This difference may lead to an inherent variability in the test, which would be shown only with a set of suitably designed studies.

Clinical implication: Perhaps the main conclusion of this review is that exercise testing research should be made more clinically relevant. Although decision analysis and predictive or Bayesian models[39] have often been used for data from exercise studies, the accuracy of the mathematic analysis is dubious because the results of current studies are so uncertain. To obtain more accurate and clinically useful measures of the sensitivity and specificity of exercise testing, investigators must give greater attention to the basic methodologic design of patient selection, data collection and data analysis.

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Peak Systolic Blood Pressure/End-Systolic Volume Ratio: Assessment at Rest and During Exercise in Normal Subjects and Patients With Coronary Heart Disease

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To assess the utility of a recently proposed index of left ventricular performance, the ratio of peak left ventricular systolic pressure to end-systolic volume, equilibrium radionuclide angiography was used to determine end-systolic volume and the systolic blood pressure obtained by cuff sphygmomanometer to determine peak systolic pressure. Data were analyzed at rest and during supine bicycle exercise in 15 normal subjects (Group I), 50 patients with coronary artery disease (Group II) and 9 patients with obstructive lung disease and no evidence of coronary artery disease on clinical examination including exercise thallium imaging (Group III). In 15 subjects the correlation between the resting angiographic and radionuclide pressure/volume ratio was excellent ($r = 0.929$, $p < 0.005$).

Forty-seven (94 percent) of the 50 patients in Group II had a depressed pressure/volume ratio at rest or an abnormal change in this ratio during exercise, whereas only 43 (86 percent) of this group had an abnormal ejection fraction at rest or during exercise. Additionally, 3 of 15 subjects in Group I had an abnormal ejection fraction response, defined as less than 0.05 ejection fraction unit increase with exercise (specificity 80 percent), whereas all subjects in Group I had a normal increase in pressure/volume ratio (specificity 100 percent). At rest, neither index identified more patients with coronary artery disease than the other. Of the nine patients in Group III, six had an abnormal ejection fraction response to exercise, whereas only one had an abnormal pressure/volume ratio response.

It is concluded that the end-systolic pressure/volume ratio is a useful index of left ventricular performance. In some patients during supine exercise stress it may be more sensitive than the ejection fraction response alone in identifying the presence of coronary artery disease.

In the hope of identifying indexes of left ventricular performance independent of loading conditions, physicians and scientists have conducted a variety of studies analyzing both the preejection and ejection phases of cardiac contraction. It has been suggested that ejection phase indexes, although load-dependent, are more useful than isovolumic indexes in distinguishing normal from abnormal contractile states.[1] However, some investigators[2,3] have proposed that analysis of ventricular function curves might better characterize the normal and failing heart than a single load-dependent index.

Recently animal experiments have shown that certain portions of the instantaneous pressure-volume loop may be load-independent. The slope of the end-systolic pressure/end-systolic volume relation has received particular attention.[4–8] Clinical applications of this observation have included manipulation of this pressure/volume ratio by either pressure or volume loading.[9] Recently the simple ratio of peak left ventricular systolic pressure to end-systolic volume was found to be a sensitive indicator of left ventricular disease alone.[10]

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To determine if this latter noninvasive index could be utilized to distinguish normal persons from patients with coronary artery disease, we evaluated 74 persons—15 normal control subjects (Group I), 50 patients with coronary heart disease (Group II) and 9 patients with severe chronic obstructive lung disease (Group III) both at rest and during supine bicycle exercise. Peak systolic blood pressure was recorded using a cuff sphygmomanometer and end-systolic volume calculated with equilibrium radionuclide angiography.

Methods

Patients: *Group I. The normal group* was composed of 10 healthy male volunteers and 5 men with atypical chest pain who had normal findings on contrast ventriculography and coronary angiography. All normal subjects had normal findings on electrocardiograms at rest and during stress, chest radiographs and physical examination and were not ingesting any medications. The mean age (± standard deviation) of this group was 49 ± 12 years (range 33 to 64).

Group II. There were 50 patients (7 women and 43 men) in the group with coronary heart disease. All underwent coronary angiography and contrast ventriculography for the evaluation of chest pain before possible aortocoronary-saphenous vein bypass graft surgery and were found to have significant coronary heart disease (70 percent or greater stenosis of a major coronary artery). The mean age of this group was 46 ± 9 years (range 32 to 61). No patient had taken any antihypertensive medication, chronic nitrate preparation or beta adrenergic blocking agent within 48 hours of the study. No patient had known peripheral vascular disease or valvular heart disease, and all had strong symmetric arterial pulses.

Ten of the 50 patients had well documented previous transmural myocardial infarction (defined as a typical history of prolonged chest pain in association with elevation of serum creatine kinase, in particular the MB fraction, with the characteristic development of Q waves greater than 0.04 second in duration on the electrocardiogram). These 10 patients all had evidence of regional akinesia on contrast ventriculography corresponding to the electrocardiographic site of infarction (anterior in 6 and inferior in 4). The other 40 patients had either normal or hypokinetic systolic shortening as assessed by visual inspection of the contrast ventriculogram. Eleven patients had single vessel disease (of the left anterior descending, coronary artery in 9 and of the right coronary artery in 2); 19 had two vessel and 20 had three vessel coronary artery disease.

Six patients were taking oral digoxin daily (mean digoxin level 1.4 ± 0.06 ng/ml), and three of the six were also taking oral furosemide daily. Virtually all of the patients with coronary artery disease required variable amounts of sublingual nitroglycerin for relief of angina pectoris but, as stated previously, none had ingested any within 48 hours of study.

Group III. The nine patients (eight men and one woman) with severe obstructive lung disease had a mean age of 46.3 ± 4 years (range 38 to 55). All of these patients had a forced expiratory volume during the first second of expiration (FEV_1) of less than 60 percent of predicted (mean 31 ± 5 percent of predicted); a mean mid expiratory flow rate between 25 and 75 percent of forced vital capacity (mean mid expiratory flow rate 25 to 75) less than 2 liters/min (mean 0.7 ± 0.4); a residual volume/total lung capacity ratio of greater than 50 percent and a resting arterial partial pressure of oxygen of less than 80 mm Hg. All patients in this group were on a stable regimen of inhaled and ingested medications prescribed by their physician. All medications were stopped at least 6 hours before the study. No patient was being treated with digitalis, beta adrenergic blocking medications, diuretic drugs or antihypertensive agents. No patient in this group had coronary artery disease, a known lipid disorder, diabetes, hypertension, or symptomatic complaints suggestive of these disorders. However, all had smoked heavily. All nine patients underwent thallium stress and 4 to 6 hour reperfusion scintigrams that were interpreted as normal by four readers. All nine patients reached at least 85 percent of the age-adjusted predicted peak heart rate. All had a normal electrocardiographic response to exercise, and exercise was stopped in all patients because of shortness of breath.

Blood pressure analysis: All blood pressures at rest and during exercise were recorded by one investigator during each individual study. The blood pressure recording was made using a Tycos® cuff and a Baumanometer® sphygmomanometer using the diaphragm of a standard stethoscope. The diaphragm was placed over the right brachial artery. (The right and left brachial systolic arterial pressures were compared and no discrepancies greater than 5 mm Hg were found.) The auscultatory pressure was obtained by inflating the cuff to a level approximately 30 mm Hg above the peak level of systolic pressure and evaluating the Korotkoff sounds. The systolic pressure was recorded as the point where the first tapping sound occurred for two consecutive beats.[11]

Exercise protocol: The details of our exercise protocol are described elsewhere.[12] After the injection and intravenous mixing of 15 to 20 millicuries of technetium-99m–labeled human serum albumin (Union Carbide or Ackerman multidose kits), a mobile scintillation gamma camera (Picker Dyna-Mo) equipped with a general purpose parallel hole collimator is placed over the patient with the detector in the modified 45° left anterior oblique position. Five minutes of scintigraphic data are acquired at rest and the basal arterial blood pressure is recorded. Each patient then performs supine bicycle exercise at gradually increasing work loads. Each exercise stage is 3 minutes in duration; at the end of each stage the patient is asked about his clinical status and the continuously monitored electrocardiographic data are reviewed. If the patient is able to continue exercising, the work load is increased. Scintigraphic data are acquired throughout the entire study and stored on videotape. To reduce the effect of varying R-R intervals on the equilibrium radionuclide time-activity curves, the scintigraphic data from the last 2 minutes of each 3 minute exercise stage are used for the calculation of left ventricular ejection fraction and left ventricular volume.

All 15 normal control subjects (Group I) and 39 of the 50 patients with coronary artery disease (Group II) stopped exercise because of fatigue; 11 patients in Group II stopped because of angina, which was associated with significant (less than 0.1 mV) electrocardiographic S-T segment depression. All patients with lung disease stopped exercising because of shortness of breath.

Radionuclide data analysis: Scintigraphic data, as well as arterial blood pressure, were obtained at rest and at peak exercise. Scintigraphic data, stored as digital pulses on videotape, were transferred to a commercially available nuclear medicine general purpose computer system (Medical Data Systems-PAD). This system divides each R-R interval into 28 equal time periods (frames) depending on heart rate, and then sums cardiac cycles at each corresponding frame to assemble a composite cardiac cycle. Each left ventricular time-activity curve was generated using a technique that allows frame by frame adjustment of the left ventricular region of interest. After the computer operator places a rectangular window around the left ventricle at the end-diastolic frame, a computer algorithm is utilized to track the edge of the left

ventricle throughout the composite cardiac cycle. The algorithm recognizes the edge of the left ventricle by a combination of the absolute count rate threshold and by the second derivative of the count rate change in each picture element. Background is automatically assigned outside the left lower quadrant of the left ventricle in the end-systolic frame.

Left ventricular ejection fraction is obtained from the background-corrected time-activity curve with use of the following equation:

$$\text{Ejection fraction} = (\text{EDC} - \text{ESC})/\text{EDC},$$

where EDC = background corrected end-diastolic counts, and ESC = background-corrected end-systolic counts.

Left ventricular end-diastolic volume and end-systolic volume are derived from the following equation:

$$\text{Volume (non-geometric units)} = \frac{\dfrac{\text{EDC or ESC}}{\text{Cardiac cycles (n)}} \times \dfrac{0.04}{\text{Actual frame time}}}{\text{Counts from 0.1 ml plasma/10 s}},$$

where cardiac cycles = total number of processed heartbeats; and counts from 0.1 ml of plasma/10 s = the radioactivity of plasma drawn from a seperate intravenous site at the time of each individual study and counted in a well counter. From a previously developed regression equation, left ventricular volume in milliliters can be calculated. This method correlates well with contrast ventriculography (r = 0.94 or greater). Detailed explanations of the theory, reproducibility and methodology can be found elsewhere.[12–16]

Correlation with contrast ventriculography: Equilibrium radionuclide angiograms were performed in the cardiac catheterization laboratory 1 hour before contrast ventriculography in 15 patients (4 from Group I and 11 from Group II). Peak systolic arterial blood pressure measured by cuff sphygmomanometer and end-systolic volume calculated by equilibrium radionuclide time-activity curves were then compared with the ratio of peak left ventricular systolic pressure to end-systolic angiographic volume as previously described.[10]

Additionally peak systolic blood pressure measured by cuff sphygmomanometer at rest and during supine exercise were then compared with simultaneous peak left ventricular pressure during the identical exercise protocol performed in the catheterization laboratory.

Left ventricular volumes were calculated from the contrast cineventriculograms using the biplane method of Sandler and Dodge,[17] and pressures were measured by means of either a Statham SF1 or a Millar Instruments 8F or 7F catheter tip micromanometer with a reference level 10 cm above the table top. The high fidelity left ventricular pressure tracing was calibrated by matching the signal with a simultaneous pressure reading obtained through the lumen or by a predetermined electronic calibration constant.

Reproducibility of the radionuclide method: Fifteen patients had a repeated equilibrium study 10 to 20 days after the initial study (without the addition or subtraction of any new medications). These 15 studies were reevaluated by the same and by one other observer to analyze inter- and intraobserver variability. For analyses of variability blood pressure was taken by both observers separately and by one observer on three separate occasions (separated by at least 10 minutes).

Statistical analysis: All correlations were performed using a least squares linear fit. Data were analyzed using the paired or unpaired Student's *t* test or, when appropriate, a repeated measures analysis of variance or simple analysis of variance.[18] All results are given as a mean ± 1 standard deviation unless otherwise specified. Abnormal resting values of ejection fraction and systolic blood pressure/end-systolic volume ratio were defined as those below the lowest data point in the normal population.

Results

Correlation with contrast angiography: The correlation between contrast and radionuclide volumes has previously been reported to be excellent (r = 0.94 or greater).[13,15] The correlation of the peak left ventricular systolic pressure/end-systolic angiographic volume ratio with the peak systolic blood pressure/end-systolic volume radionuclide ratio in the 15 patients who underwent both studies was excellent (r = 0.929) (Fig. 1). Additionally, peak left ventricular systolic pressure correlated well with systolic blood pressure (r = 0.90); as expected, the brachial arterial systolic pressure was 14 to 19 mm Hg greater than the simultaneously recorded left ventricular pressure. Simultaneous left ventricular systolic pressure and systolic blood pressure by cuff sphygmomanometer at peak exercise also correlated well with each other (r = 0.88), and under these conditions the brachial pressure was 18 to 23 mm Hg greater than the left ventricular pressure.

Vital signs and work loads during exercise: There was no significant difference between resting heart rate or systolic blood pressure when the normal control subjects (Group I) and the patients with coronary artery disease (Group II) were compared (73 ± 9 beats/min and 128 ± 6 mm Hg, respectively, in Group I and 76 ± 12 beats/min and 131 ± 7 mm Hg in Group II). The

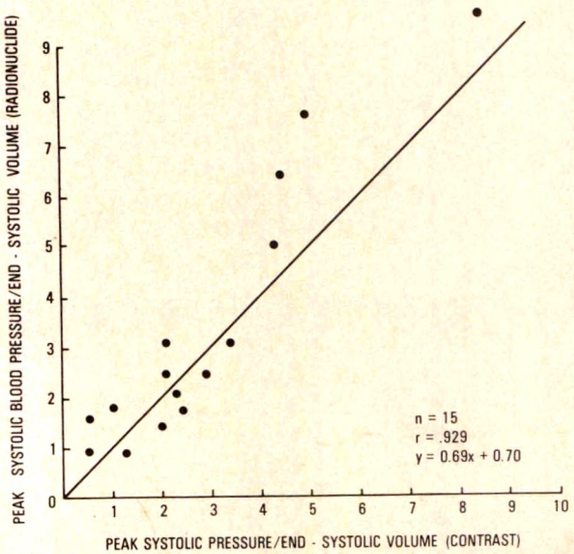


FIGURE 1. Comparison of the ratio of peak systolic blood pressure (mm Hg) obtained with cuff sphygmomanometry to end-systolic volume obtained with equilibrium radionuclide angiography and the pressure/volume ratio obtained at cardiac catheterization (ratio of peak systolic left ventricular pressure to angiographic end-systolic volume). The line of identity is given. The noninvasive data points tend to fall above the line because the systolic blood pressure is greater than left ventricular systolic pressure. See text for discussion.

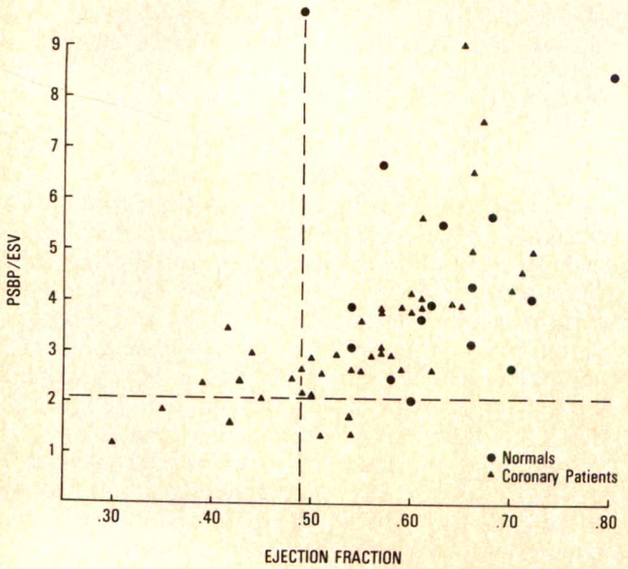


FIGURE 2. Comparison of the results at rest for the peak systolic blood pressure/end-systolic volume ratio (PSBP/ESV) and left ventricular ejection fraction in the 50 patients with coronary artery disease (Group II) and the 15 normal subjects (Group I). The **dashed lines** indicate the lower limit of normal for either value.

normal subjects in Group I exercised to a peak heart rate of 151 ± 24 beats/min and a systolic blood pressure of 205 ± 11 mm Hg; these values were significantly greater than the respective values (131 ± 19 beats/min and 193.1 ± 14 mm Hg; both p <0.01) in Group II. The normal group exercised to a peak work load (kp-m) of 738 ± 175, which was significantly greater (p <0.005) than that achieved by Group II (514 ± 205 kp-m).

The patients with chronic obstructive lung disease (Group III) had a mean resting heart rate of 75 ± 11 beats/min, and resting systolic blood pressure of 129 ± 4 mm Hg; these values were not significantly different from those in Group I or II. Their exercise time was briefer than that of the normal subjects in Group I but similar to that of the patients with coronary disease in Group II. The group attained a heart rate of 154 ± 18 beats (p <0.01 versus Group II and not significant [NS] versus Group I), systolic blood pressure of 189.4 ± 11 mm Hg (p = NS versus Group II and <0.01 versus Group I) and a work load of 495 ± 175 kp-m (p = NS versus Group II and <0.005 versus Group I).

Resting hemodynamic data: The mean radionuclide left ventricular ejection fraction in the normal patients in Group I was 0.61 ± 0.06; this value was significantly greater than that in the patients with coronary heart disease in Group II (0.56 ± 0.10 p <0.05), but not different from that in the patients with lung disease in Group III (0.60 ± 0.14). Nine patients in Group II had an ejection fraction below the lower limit of normal (less than 0.49), and seven had a peak pressure/end-systolic volume ratio below the lower limit of normal (less than 2.1) (Fig. 2). Five of these patients with a depressed resting ejection fraction had a normal ratio, whereas three with a depressed ratio had a normal ejection fraction. One patient in Group III had both a depressed ejection fraction and a depressed pressure/volume ratio.

All five patients in Group II with a depressed ejection fraction and a normal ratio had a resting systolic blood pressure greater than 140 mm Hg at the time of the initial study (mean 153 ± 6 mm Hg); this mean was significantly greater (p <0.005) than that of the remaining patients in Group II (129 ± 9 mm Hg). It was also significantly greater (p <0.05) than that of a small subgroup of three patients in Group II with a depression of both resting ejection fraction and peak pressure/end-systolic volume ratio (127 ± 3 mmHg). The five patients in Group II just described had normal left ventricular end-diastolic pressure, slightly increased left ventricular end-diastolic volume (greater than 90 ml/m^2) and diffuse as opposed to merely regional hypokinetic wall motion abnormalities.

The three patients with a normal ejection fraction and depressed resting ratio had a lower mean peak systolic blood pressure than that of the remaining patients in Group II (114 ± 3 versus 132 ± 6 mm Hg, p <0.01) (Fig. 2). These patients had elevated left ven-

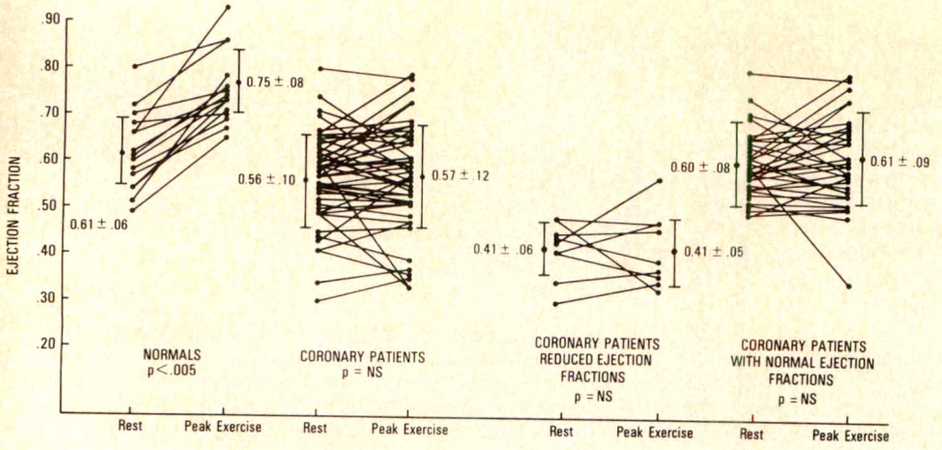


FIGURE 3. Change in left ventricular ejection fraction during supine exercise. Note the increase in the group mean of the normal patients (Group I) and the lack of change in the patients with coronary artery disease (Group II). However, 3 of the 15 normal subjects did not have an increase in ejection fraction of 0.05 unit or more.

tricular end-diastolic pressure and marked regional and global wall motion abnormalities. The one patient in Group III with an abnormal value at rest had a normal resting blood pressure (127/83 mm Hg).

Exercise data: ejection fraction: *Twelve (80 percent) of the 15 normal subjects (Group I)* had a significant increase (0.05 or greater ejection fraction unit) in left ventricular ejection fraction with exercise. All three who did not increase their ejection fraction had atypical chest pain and normal contrast studies. In Group I as whole, the mean peak exercise left ventricular ejection fraction was 0.75 ± 0.08, which was significantly greater than the resting value of 0.60 ± 0.06 ($p < 0.005$) (Fig. 3). In association with this change in ejection fraction, end-systolic volume declined from 37.5 ± 11.8 ml at rest to 19.1 ± 5.1 ml at peak exercise ($p < 0.005$) (Fig. 4). All normal subjects attained a peak exercise ejection fraction of 0.64 or greater.

Eighteen (36 percent) of the 50 patients in Group II with coronary artery disease had a greater than 0.05 increase in ejection fraction unit (mean 0.09 ± 0.03) with exercise. Four of these 18 had an abnormally depressed resting ejection fraction. With use of the following criteria for an abnormal study: (1) resting left ventricular ejection fraction less than 0.49; (2) an increase in ejection fraction of less than 0.05 unit during exercise, or (3) a peak exercise ejection fraction of less than 0.64, a total of 43 (86 percent) of the 50 patients in Group II had an abnormal exercise ejection fraction at rest or during exercise (Fig. 3). Twenty subjects in the total study had a resting ejection fraction of 0.65 or greater; 15 of these were in Group II and 5 in Group I. In 14 of the 15 patients in Group II and in 2 of the 5 in Group I ejection fraction failed to increase by 0.05 unit with exercise. Thus, it is possible that different criteria for a normal exercise response will be required in subjects with an elevated ejection fraction. The normal subjects with a high ejection fraction and a subnormal increase in ejection fraction with exercise all had a normal increase in pressure/volume ratio.

Four subjects had a depressed resting ejection fraction, and increased their ejection fraction by 0.05 unit or more with exercise. These patients did not experience new S-T depression, angina or hypotension during exercise. All stopped exercising because of fatigue. Of 41 patients with coronary artery disease who had a normal resting ejection fraction, 34 (83 percent) had either less than a 0.05 increase in ejection fraction unit with exercise or did not attain a peak exercise ejection fraction of 0.64 or more.

Six of the nine patients in Group III with obstructive lung disease had a less than 0.05 unit increase in left ventricular ejection fraction with supine bicycle exercise or had a resting ejection fraction of less than 0.49 (Fig. 5). All nine patients had at least a 10 ml decrease in end-systolic volume and end-diastolic volume with exercise, along with a decrease in stroke volume.

Exercise data: peak systolic pressure/end-systolic volume ratio: All 15 normal subjects had an increase in pressure/volume ratio with exercise, from 3.41 ± 2.20 at rest to 10.71 ± 6.20 at peak exercise ($p < 0.001$)

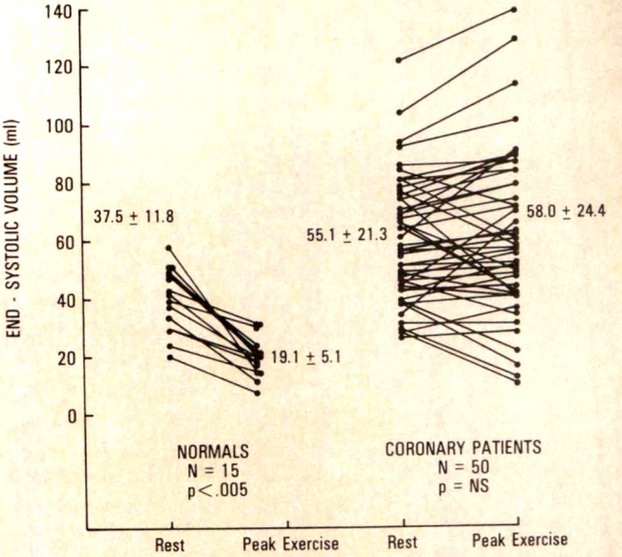


FIGURE 4. Response of end-systolic volume to exercise in the normal patients (Group I) and the patients with coronary artery disease (Group II). Note the marked decline in normal subjects, whereas only 8 of 50 patients with coronary artery disease had a decrease in volume of more than 10 ml.

(Fig. 6). They all had a peak exercise ratio of 4.8 or greater, a peak exercise increase in the pressure/volume ratio of 85 percent or greater above the resting value, and a resting ratio 2.10 or greater.

Forty-seven (94 percent) of the 50 patients with coronary artery disease in Group II had either: (1) a resting ratio of less than 2.10; (2) an increase of the peak systolic pressure/end-systolic volume ratio at peak exercise of less than 85 percent over the resting value; or

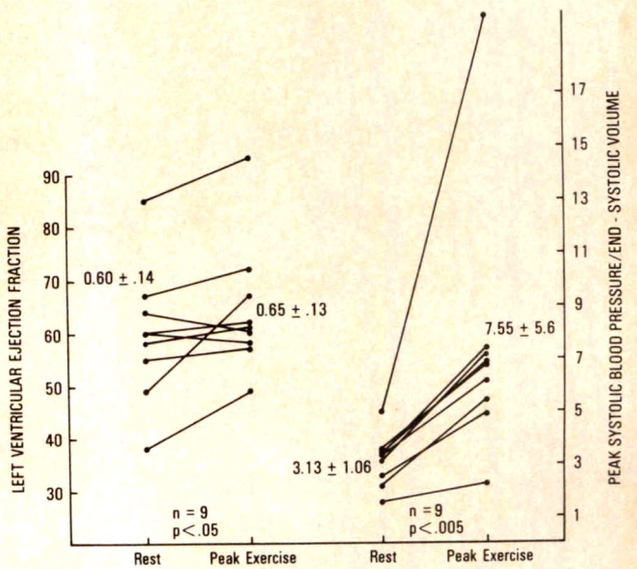


FIGURE 5. Ejection fraction and pressure/volume ratio at rest and at peak exercise in the nine patients with severe obstructive lung disease (Group III).

(3) a ratio at peak exercise of less than 4.8. (Fig. 6). Seven patients in Group II had a reduced resting pressure/volume ratio; in all seven the ratio failed to increase by 85 percent. Of the remaining 43 subjects, 40 (93 percent) did not increase their ratio by 85 percent or attain a peak exercise value of 4.8 or more. In contrast in Group III eight of the nine patients with severe obstructive lung disease had a normal increase in pressure/volume ratio with exercise (Fig. 5).

Exercise data: end-systolic volume response: All normal subjects in Group I showed a decrease in end-systolic volume with exercise from a mean of 37.5 ± 11.8 to 19.5 ± 5.1 ml ($p < 0.005$). The minimal absolute decrease in end-systolic volume was 10 ml, and the minimal percent decline in end-systolic volume compared with the value at rest was 25 percent (Fig. 4).

Forty-two (84 percent) of the 50 patients with coronary disease in Group II had either an increase or a less than a 10 ml decrease in end-systolic volume with exercise. The remaining seven patients included two patients with isolated right coronary artery disease, two with two vessel disease and four with three vessel disease. None of these latter patients exhibited pain or S-T segment changes with exercise. As noted, in all patients with lung disease (Group III), end-systolic volume decreased by at least 10 ml with exercise.

Reproducibility: Fifteen patients in Group II had a second equilibrium study a mean of 14.9 days after the first study (range 10 to 20). The results of the two temporally separated pressure/volume ratios correlated well ($r = 0.94$) with a small variation (±0.31, range 0.14 to 0.69).

The intraobserver variability was small (±0.24, range 0.07 to 0.51, $r = 0.97$), as was the interobserver variability (±0.29 range 0.10 to 0.53, $r = 0.96$). The variability of three different recordings of systolic pressure, taken 10 minutes apart, was ±5.1 mm Hg (range 0 to 11). This comparison was made by removing the blood

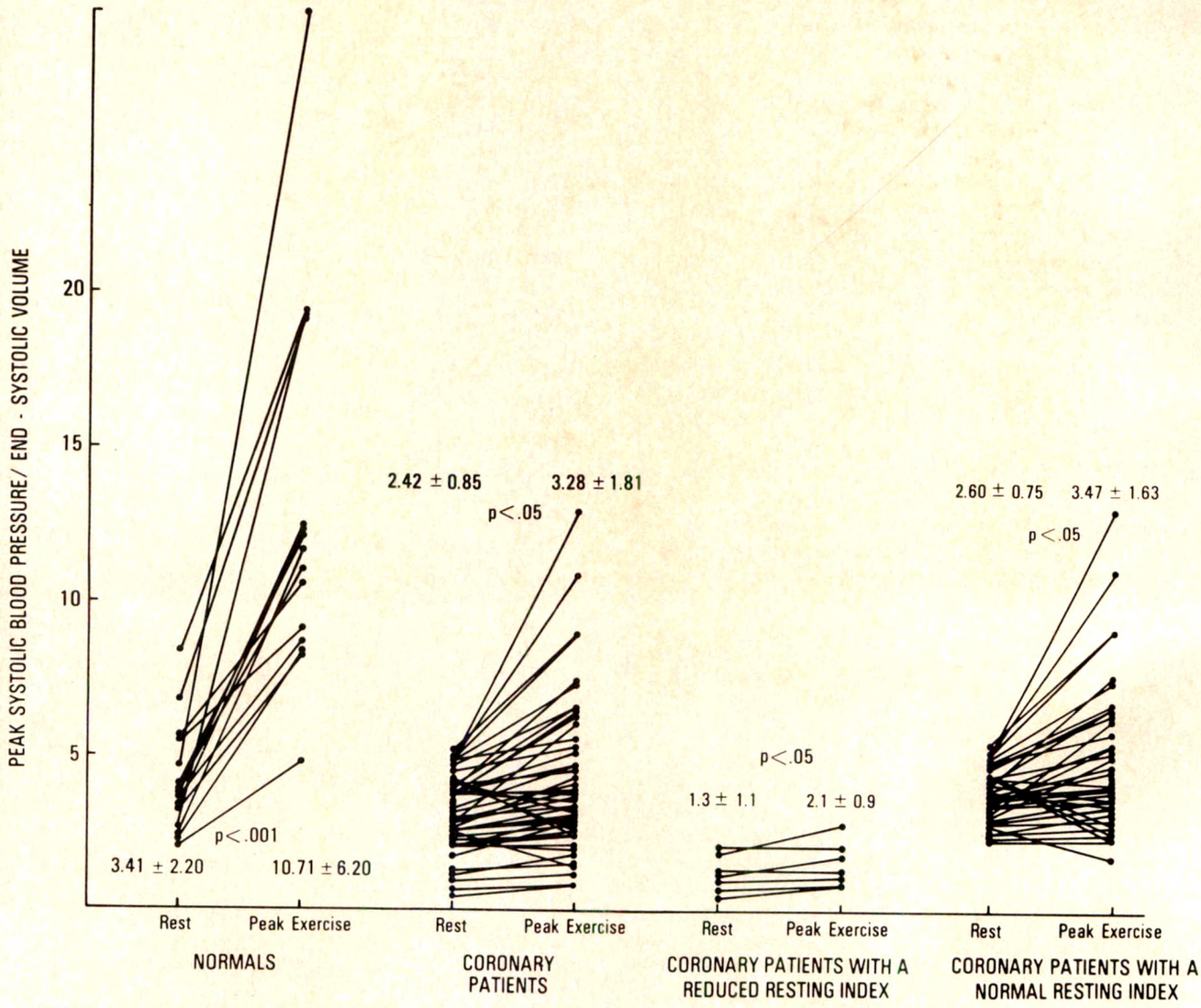


FIGURE 6. Response of the pressure/volume ratio in the 15 normal subjects and 50 patients with coronary artery disease. See text.

pressure cuff, replacing it and then obtaining another pressure reading.

Utility of the test: To determine the usefulness of these two analyses of left ventricular performance during exercise (response of ejection fraction [EF] and peak systolic pressure [PSP]/end-systolic volume [ESV] ratio), the following standard calculations were made for Group I (normal subjects) and Group II (patients with coronary artery disease):

$$(1)\ \text{Specificity} = \frac{\text{Number of subjects in Group I with normal exercise EF or PSP/ESV response}}{\text{Total number of subjects in Group I}}$$

$$(2)\ \text{Sensitivity} = \frac{\text{Number of patients in Group II with an abnormal response}}{\text{Total number of patients in Group II}}$$

$$(3)\ \text{Predictive accuracy} = \frac{\text{True positive tests (coronary disease and abnormal response)}}{\text{All positive tests}}$$

For the ejection fraction exercise response, with exclusion of the patients with obstructive lung disease, the sensitivity for coronary disease was 86 percent, the specificity 80 percent and the predictive accuracy 93 percent. For the pressure/volume response the sensitivity was 94 percent and the specificity and predictive accuracy were 100 percent. With exclusion of the patients with a depressed resting ejection fraction, the ejection fraction response during exercise had a sensitivity of 83 percent. With exclusion of the patients with a depressed resting pressure/volume ratio, the pressure/volume response to exercise had a sensitivity of 93 percent.

Discussion

Commonly used indexes of left ventricular performance involve analysis of the ejection phase of the cardiac cycle. Recent investigators have suggested that evaluation of the relation of end-systolic pressure to end-systolic volume might prove more valuable than typical ejection phase indexes such as the ejection fraction.[4–10] Their studies in dogs and in human beings involved the use of left ventricular pressure catheters and either ultrasonic crystals or contrast ventriculography. To attempt a noninvasive analysis of this index, we utilized previously described and well validated radionuclide methods to calculate left ventricular end-systolic volume and ejection fraction.[13–15] Peak systolic blood pressure obtained with a cuff sphygmomanometer was utilized as a close approximation of peak systolic left ventricular pressure. The correlation of the noninvasively obtained index with a virtually simultaneous contrast angiographic result was excellent ($r = 0.929$) as were reproducibility and intraobserver and interobserver variation. However, no patient with valve insufficiency or stenosis or overt peripheral vascular disease was studied. The results were then analyzed at rest and at peak exercise during supine bicycle stress.

Pressure/volume ratio versus ejection fraction responses: At rest, the pressure/volume ratio was no more sensitive than the ejection fraction in identifying patients with coronary artery disease. However, when the indexes were discordant, the ejection fraction tended to be abnormal in the setting of an elevated blood pressure and normal in the presence of a normal blood pressure, thus implying that the level of arterial pressure influences this ejection phase index. During exercise, the pressure/volume response appeared to be more sensitive for identifying the presence of left ventricular dysfunction (excluding the lung disease patients) and, thus, coronary artery disease (94 versus 86 percent for ejection fraction response). Additionally, the specificity was better for the pressure/volume ratio (100 versus 80 percent for the ejection fraction response). These ejection fraction results are similar to the data reported recently by Borer et al.,[19] who found a sensitivity of 89 percent for the ejection fraction response with exercise. They and others[20,21] also found that patients with chest pain and normal coronary arteries may not have an increased ejection fraction with exercise, although they still meet other "normal" criteria.[19]

We[22] have previously noted abnormalities in the ejection fraction response to supine exercise in patients with obstructive lung disease. In our study we found a decline in left ventricular size with exercise, probably due to an elevation in right ventricular outflow impedance and a decline in right ventricular stroke volume with exercise. Nonetheless, alterations in loading conditions did not significantly alter the pressure/volume response to exercise in this group of patients.

Limitations of method: The limitations of the method rest with the variability of the radionuclide technique and the accuracy with which the peak systolic blood pressure can represent the peak left ventricular systolic pressure. As seen in Figure 1, the noninvasive result tends to overestimate the actual ratio, in large part because the brachial arterial pressure reflects an amplified left ventricular pressure wave secondary to the rheologic properties of the arterial tree, that is, arterial compliance and pressure waveform reflectance.[23] Patients with coronary vascular disease are more likely than normal subjects to have some degree of peripheral vascular disease,[24] and this difference may lead to overestimation of the peak left ventricular systolic pressure in these patients. These considerations may in part explain the difference between our data and the results of Nivatpumin et al.,[10] who found the resting pressure/volume ratio more useful than the ejection fraction. This decrease in arterial compliance would tend to exaggerate the blood pressure response to exercise, and sway the results away from identifying patients with coronary disease. However, both acute and chronic decreases in arterial compliance are known to depress left ventricular ejection and function,[24–29] and might tend to magnify the abnormal change in ejection fraction during exercise through an altered impedance effect in patients with coronary disease. This effect would, of course, contribute to changes in left ventricular volume during exercise.

Implications: The systolic blood pressure/end-systolic volume ratio is a reproducible method of assessing left ventricular performance during exercise, and may

be more sensitive than ejection fraction for identifying the presence of left ventricular dysfunction during exercise. This sensitivity is well illustrated by the abnormal ejection fraction response to exercise in the five patients with chronic lung disease who had a normal pressure/volume ratio at peak exercise. However, our patients were highly selected for the presence or absence of coronary heart disease, and the assessment of the utility of the pressure/volume ratio will require further investigation in larger groups of patients.

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Influence of Coronary Artery Disease on Pulmonary Uptake of Thallium-201

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An increased pulmonary thallium-201 concentration has been observed in exercise stress thallium perfusion imaging in patients with coronary artery disease. To understand the cause of this lung uptake, studies were performed in experimental animals and in patients undergoing stress thallium perfusion imaging. The extraction fraction of thallium-201 by the lungs was measured in a group of eight dogs using a dual isotope technique. Basal thallium-201 extraction fraction at rest was 0.09 ± 0.009. After administration of isoproterenol, it decreased to 0.06 ± 0.02 (difference not significant). After balloon obstruction of the left atrium (which increased mean left atrial pressure and pulmonary transit time) and after administration of acetylcholine as a bolus injection (which prolonged pulmonary transit time only) it increased to 0.19 ± 0.02 ($p < 0.01$).

Lung thallium-201 activity was measured in 86 patients who had undergone cardiac catheterization and stress-redistribution myocardial perfusion imaging. The initial/final lung activity ratio was 1.41 ± 0.03 in patients with no significant coronary artery disease, 1.52 ± 0.03 (difference not significant) in patients with single vessel coronary disease, 1.60 ± 0.05 ($p < 0.05$) in those with two vessel disease and 1.59 ± 0.05 ($p < 0.05$) in those with triple vessel disease. Quantitation of lung activity in 30 of these patients indicated that the increased ratio in patients with multivessel coronary artery disease was due to a transient absolute increase in the thallium-201 concentration immediately after maximal exercise. The data imply that increased pulmonary concentration of thallium-201 during exercise is a consequence of left ventricular failure.

Since the introduction of thallium-201 in 1973[1] as an imaging agent for the evaluation of coronary artery disease,[2–4] a major criterion for ischemia has been the presence of stress-induced focal areas of decreased myocardial tracer concentration, which are normal or near normal with injection at rest. In 1975, the change in the relative redistribution of thallium-201 within the myocardium over a period of time was shown to accurately separate regions of scar from relatively low flow.[5]

The lungs have received scant attention in the interpretation of thallium-201 studies, although they contribute a considerable portion of the background activity of the heart.[6] We have observed greatly increased pulmonary thallium-201 activity immediately after exercise testing in some patients with coronary artery disease, which then decreased to normal in images obtained 2 to 3 hours later.

This study was initiated to determine (1) if increased lung thallium-201 activity in animals could be caused by experimentally induced alterations in transit time or pulmonary arterial pressure, and (2) the relation of thallium-201 lung activity to the presence of coronary artery disease.

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Methods

Animal Studies

Experimental preparation: Adult mongrel dogs, weighing 12 to 26 kg, were anesthetized with intravenous sodium pentobarbital, 30 to 35 mg/kg body weight, supplemented with 6 mg/kg as necessary; they were intubated and placed on a Harvard pump respirator. Polyethylene catheters were inserted into the jugular vein for injection of isotopes into the right heart chambers, into the carotid artery for arterial blood sampling and into the femoral artery for monitoring of arterial pressure. A thermistor tip flow-directed catheter was placed in the pulmonary artery for monitoring of pulmonary arterial pressure and cardiac output. A Foley catheter with a 30 cc balloon was inserted into the left atrium to provide a means of acutely increasing pulmonary venous pressure.

Interventions to change pulmonary transit time: Baseline measurements were performed in eight dogs. The following conditions were then produced: (1) infusion of isoproterenol (six dogs); (2) hypoxia (inspired 5 percent oxygen) (six dogs); (3) left atrial obstruction (six dogs); and (4) bolus injection of acetylcholine (three dogs).

The isoproterenol infusion was used to create conditions of decreased pulmonary transit time without a significant change in mean pulmonary arterial pressure.[7] The infusion was performed at a rate sufficient to increase heart rate by at least 20 beats/min.

Hypoxia was used to increase mean pulmonary arterial pressure with less change in cardiac output. The inspired oxygen was decreased to 5 percent while a fixed respiratory rate was maintained.

Left atrial obstruction was used to prolong pulmonary transit time and to increase mean pulmonary arterial pressure. It was induced by obstruction to mitral inflow produced by inflating a Foley catheter in the left atrium for 5 minutes.

Injection of 0.5 to 2 mg of acetylcholine into the pulmonary artery was used to increase pulmonary transit time and decrease mean pulmonary arterial pressure. With this intervention, the extraction fraction was evaluated in response to increasing doses of acetylcholine and the changes in extraction fraction related to alteration in the electrocardiographic R-R interval because accurate cardiac output determinations cannot be obtained by thermodilution under circumstances of rapid change in heart rate.

Extraction fraction of thallium-201 by the lungs: This fraction was determined using a double isotope dilution method[8,9] during initial transit of a bolus injection of a mixed tracer through the lungs. This technique uses the bolus injection of thallium-201 mixed with iodine-125–labeled human serum albumin (Mallinckrodt, Inc.) into the right heart chambers and sampling from the carotid artery. The assumption was made that none of the albumin was removed by the lungs[10] so that any change in the ratio of thallium-201 to iodine-125 was due to the extraction of thallium by the lung. Sequential arterial blood samples were collected at 3 second intervals for a 40 second period starting at the time of tracer injection. Measurements of mean pulmonary arterial pressure and thermodilution cardiac output were recorded at the time of blood sampling. Aliquots of the injectate and the blood samples, after weighing, were counted in a 5-inch (12.7 cm) diameter sodium iodide scintillation counter, using windows of 70 to 200 keV for thallium-201 and 15 to 55 keV for iodine-125. Standards for each radioisotope were counted in each window, and ratio corrections were made for the activity from each isotope appearing in the other window. Less than 20 percent of the counts in the iodine window were due to thallium-201 crossover. The extraction fraction (F_{ex}) was calculated by the formula:

$$F_{ex} = \frac{\text{Injected ratio} - \text{Sampled ratio}}{\text{Injected ratio}}$$

An instantaneous extraction fraction was calculated from each 3 second blood sample. In addition, an extraction fraction was calculated by integration of the counts from the initial appearance of the indicator through to the sample where the iodine-125 albumin concentration had decreased to one third of the peak concentration. One third of the peak was selected to encompass the majority of the bolus dose of activity and to minimize contribution to the bolus dose by recirculation. This method can be utilized when extraction fractions are less than 0.3.[11]

The fractional extraction of thallium-201 by the lungs was compared with the logarithm of cardiac output for all interventions except acetylcholine and to the logarithm of the R-R interval for the acetylcholine studies.

Patient Studies

Patients: Eighty-six patients (69 men and 17 women aged 22 to 70 years) were studied. They were referred for thallium-201 stress myocardial imaging for evaluation of chest pain without evidence of valvular heart disease, and underwent coronary angiography within 3 months of imaging.

Exercise stress testing with thallium-201 imaging: A multistage exercise treadmill test was performed using the Bruce protocol[12] with continuous monitoring of the electrocardiogram and blood pressure until one of the following five criteria was reached: significant angina pectoris, fatigue, three consecutive ventricular premature beats, achievement of at least 85 percent maximal predicted heart rate, or more than 2 mm of horizontal or downsloping S-T depression appearing on the exercise electrocardiogram. At that point, thallium-201 was administered intravenously and exercise continued for a further 45 seconds. Imaging in the supine position was initiated within 4 minutes of exercise with images obtained in the anterior, 50° left anterior oblique, and 70° left anterior oblique projections. Approximately 2 1/2 hours after the exercise test, a second set of images was obtained.

Imaging was performed with a standard field of view gamma camera (Ohio Nuclear Series 100) equipped with a low-energy, general all-purpose, parallel hole collimator, utilizing a 20 percent window centered around the mercury X-ray film peak of thallium-201. Data were acquired in a dedicated nuclear medicine data system (Ohio Nuclear VIP 450) for a preset time. In 30 patients who underwent imaging at 7 minutes/view, the thallium-201 dose was precisely measured at 2.0 millicuries (mCi) in a radioisotope calibrator. The remaining patients received 1.5 to 2.2 mCi of thallium.

Coronary angiography: Selective coronary angiography in multiple views was performed in all patients using either the Judkins or Sones technique. The extent of coronary arterial stenosis was determined from the most severe lesion in a vascular distribution. An artery was considered significantly narrowed when a lesion compromised the luminal diameter by 50 percent or more in at least two different projections.

The severity of coronary artery disease was categorized as follows: 0, no significant coronary disease; 1, single vessel disease (more than 50 percent narrowing) involving either the left anterior descending, left circumflex or right coronary artery; 2, disease involving two of these vessels; and (3) disease involving all three vessels.

Analysis of thallium images: The initial and delayed thallium-201 images were analyzed by placing a region of interest in the anterior view to outline the lung, superior to the

anterolateral wall of the myocardium (Fig. 1). The number of counts/picture element of lung was determined, and the ratio of these counts between the initial and the delayed image determined. In the 30 patients given an exact dose of thallium-201, the counts/cm^2 in the lung were used as an approximation to the absolute thallium-201 uptake in lung and compared with the extent of coronary artery disease.

Results

Animal Studies

The physiologic changes caused by the interventions are shown in Table I. Isoproterenol caused a significant increase in cardiac output (from 0.15 to 0.22 liters/min per kg) with no significant change in the mean pulmonary arterial pressure. Hypoxia caused no change in the cardiac output, but increased the mean pulmonary arterial pressure from a mean of 13 to 19 mm Hg ($p < 0.05$). Left atrial obstruction reduced the cardiac output from 0.15 to 0.07 liters/min per kg and increased the mean arterial pressure from 13 to 21 mm Hg ($p < 0.01$).

Pulmonary extraction fraction of thallium: The mean extraction fraction of thallium-201 by the lungs in the basal state was 0.09 ± 0.009 (mean ± standard error of the mean). The pulmonary extraction did not change significantly with isoproterenol or hypoxia. Left atrial obstruction and acetylcholine injection caused an increase in extraction to values of 0.19 ± 0.024 and 0.19 ± 0.017, respectively ($p < 0.01$).

The extraction fraction for the interventions correlated linearly with the logarithm of the cardiac output per unit weight of the dog ($r = -0.58$, $p < 0.01$), although the effect of acetylcholine has been excluded because the cardiac output was not measured. The response of the measured physiologic variables to a bolus injection of acetylcholine introduced into the pulmonary artery is shown in Figure 2 as a variable period of asystole followed by a prolonged period of bradycardia. Immediately after a bolus injection of acetylcholine, tracer in the pulmonary circulation will be in contact with the pulmonary capillary epithelium for a prolonged period owing to the cardiac standstill followed by bradycardia. Thermodilution measurements of cardiac output during this period are liable to substantial inaccuracy, and for this reason the length of the R-R interval during the period of asystole as a measure of the prolongation of pulmonary transit time. Because the relation between this variable and the extraction fraction was unlikely to be a linear function, the logarithm of this period was used for comparison. The correlation between the logarithm of the R-R interval and the extraction fraction was 0.88 ($p < 0.01$).

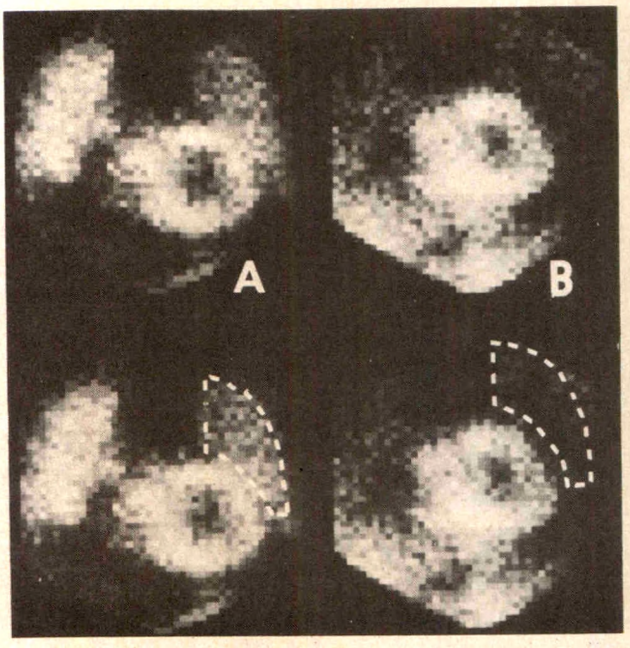


FIGURE 1. Thallium-201 images obtained in the anterior projection immediately (**A**) and 2 1/2 hours (**B**) after exercise. A region of interest has been placed over the lung superolaterally to the anterior wall of the left ventricle.

Comparison of the mean pulmonary arterial pressure with the extraction fraction demonstrated that there was a significant, although modest, correlation ($r = 0.37$, $p < 0.01$). Once again, results from the acetylcholine intervention have not been included because the mean pulmonary arterial pressure, although always reduced during the resultant asystole, was too variable to measure accurately.

In three of the dogs with four measurements of extraction fraction during atrial obstruction, the phasic pulmonary arterial pressure was measured so that the end-diastolic pressure could be determined and used as an indication of left atrial pressure. There was a significant correlation between the extraction fraction and

TABLE I

Physiologic Responses in Lung Extraction Fraction in Dogs Subjected to Intervention

Condition	Cardiac Output (ml/min per kg)	Mean Pulmonary Arterial Pressure (mm Hg)	Mean Heart Rate (beats/min)	Extraction Fraction
Baseline	0.15 ± 0.02	13.2 ± 1.1	167	0.090 ± 0.009
Isoproterenol	0.22 ± 0.02 (↑49%)†	13.8 ± 1.3 (↑5%)	195*	0.062 ± 0.019
Hypoxia	0.17 ± 0.02 (↑16%)	19.3 ± 2.4 (↑46%)*	146	0.077 ± 0.019
Left atrial obstruction	0.07 ± 0.01 (↓47%)†	21.5 ± 2.3 (↑63%)†	147	0.19 ± 0.024†
Acetylcholine				0.19 ± 0.017†

* $p < 0.05$. † $p < 0.01$.

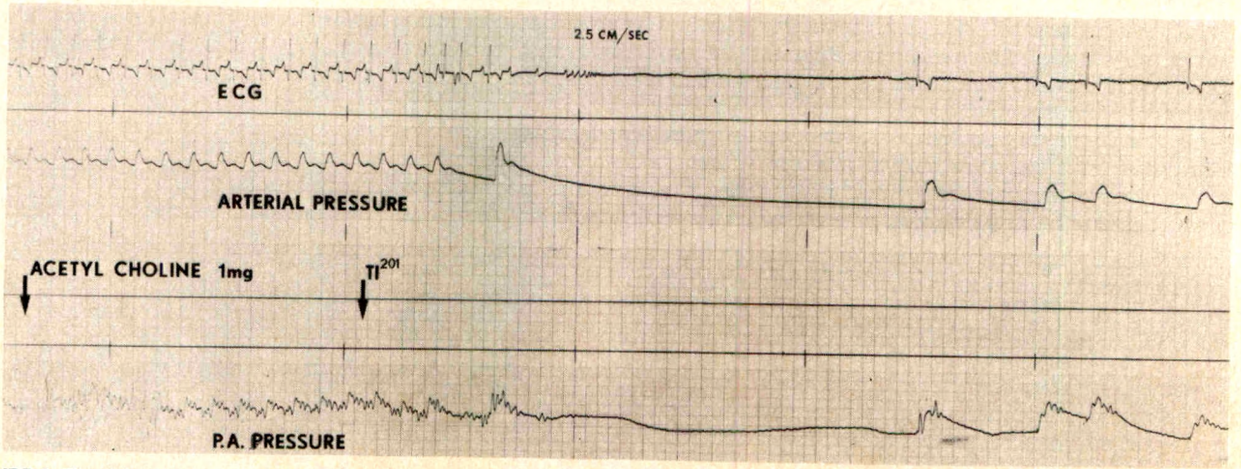


FIGURE 2. Physiologic tracing illustrating the response of the electrocardiogram (ECG), arterial blood pressure and pulmonary arterial (P.A.) pressure to the administration of a bolus injection of acetylcholine (**first arrow**) into the pulmonary artery. Tl^{201} = thallium.

the end-diastolic pulmonary arterial pressure ($r = 0.76$, $p < 0.05$).

Patient Studies

The relation between the extent of coronary artery disease and exercise performance is shown in Table II. The patients with coronary artery disease achieved lower mean heart rates than the group without significant coronary disease, although heart rates were significantly different from rates in the control group only in patients with double and triple vessel disease ($p < 0.01$). Similarly, the duration of exercise in the group with double and triple vessel disease was significantly different ($p < 0.01$) from that in the group without coronary artery disease.

Thallium lung activity in patients with coronary artery disease: The relation between the extent of coronary artery disease and the initial/final lung ratio of thallium-201 (Fig. 3) shows that the ratio was 1.41 ± 0.03 in the group with no coronary artery disease, 1.52 ± 0.03 in the group with single vessel disease (p = not significant), 1.60 ± 0.05 in the group with two vessel disease ($p < 0.05$) and 1.59 ± 0.05 in the group with triple vessel disease ($p < 0.05$).

TABLE II

Data on Patients Subjected to Upright Thallium-201 Stress Perfusion Imaging

Vessels With Coronary Disease (n)	Patients (n)	Mean Age (yr)	Mean Maximal Heart Rate (beats/min)	Mean Exercise Time (min)	Initial/ Final Lung Ratio
0	19	46	162	9.0	1.41
1	11	51	152	7.6	1.52
2	31	54*	135†	6.5†	1.60*
3	25	55†	123†	6.0†	1.59*

* $p < 0.05$. † $p < 0.01$.

The results in the group of 30 patients who were given precise quantities of thallium-201 and imaged for a preset time are shown in Figure 4. In all three groups with coronary artery disease initial lung activity was significantly higher than in the group with no disease ($p < 0.05$), but this difference had disappeared in the delayed images except for the group with single vessel disease ($p < 0.05$). The mean rate of clearance from the lungs was faster in those with coronary artery disease ($p < 0.05$).

Discussion

Factors influencing lung extraction of thallium: Crone's investigation[13] of the organ extraction of test substances showed that the significant factors were the permeability of the capillaries, the surface area available for exchange and the rate of blood flow. These variables are related by the equation

$$P = (Q/A) \times \log_e \frac{1}{1 - E},$$

where P = permeability of the organ, Q = blood flow, A = surface area of capillaries, and E = initial extraction.

From this equation, one would expect a logarithmic relation between blood flow and extraction; we therefore used the logarithm of the cardiac output in our data analysis. Crone demonstrated that the organ extraction of inulin and sucrose varied considerably among organs, but for both substances was very small when the lung was considered. However, the extraction levels of ethanol[14] and water[15] were very high. The extraction fraction of small cationic ions, such as sodium, was investigated by Pearce,[16] who showed that under control conditions there was virtually complete recovery of the sodium indicator by comparison with that of an intravascular marker (iodine-131–labeled human albumin), but recovery was increased significantly in conditions of pulmonary edema. Although the extraction of thallium-201 might be expected to be similar to that of so-

dium because it is also a small cation, the difference in ionic diameter is likely to create an alteration in its permeability through body tissues. Measurement of the extraction fraction of thallium-201 by the lungs has not yet been reported.

Factors causing increased thallium accumulation in lungs in coronary artery disease: Not only was the ratio of initial/final pulmonary thallium-201 activity greater in patients with multivessel coronary artery disease, but also there was an absolute increase in the initial pulmonary activity as shown in the patients given equivalent amounts of thallium. Increased thallium accumulation in the lungs could be caused by several factors. First, the recent study by Okada et al.[17] demonstrated that, in the supine exercising patient with coronary artery disease, there is a transient increase in pulmonary blood volume. Thus, transient retention of thallium-201 in this increased pulmonary blood pool could give rise to an apparent increase in lung thallium-201 activity. However, thallium-201 clears rapidly from the blood pool with a half-life of less than 1 minute,[18] and the half-life after injection during stress should be shorter, because 65 percent of the thallium dose is extracted per circulation time.[8] Close inspection of the left ventricular cavity in our patients with elevated lung uptake showed no obvious thallium content.

The equation derived by Crone[13] indicates that an increase in extraction fraction is to be expected with a decrease in flow rate through the lungs. The pulmonary transit time is related to the pulmonary blood volume by the following relation: pulmonary blood volume = cardiac output (ml/s) × pulmonary mean transit time.[19] In coronary artery disease, the cardiac output is known to reach a plateau, if not actually to decrease, when cardiac decompensation supervenes.[20] Thus, from this last equation it can be seen that the mean pulmonary transit time may increase at peak stress, resulting in prolongation of thallium-201 contact with the pulmonary endothelium. The increased extraction fraction associated with the prolonged transit time caused by acetylcholine in dogs but without an increase in pulmonary arterial pressure indicates that increased lung thallium accumulation can occur without an increase in pulmonary arterial pressure. The converse, decreased extraction when flow is increased, could not be proved in our experiments because the error with low fractional extractions becomes excessive when the extraction fraction decreases below 0.05.[21]

Another possible cause of increased lung uptake is the development of increased left atrial pressure in association with the occurrence of subclinical left ventricular failure during exercise in patients with coronary artery disease. The effect of pressure on transcapillary exchange between vascular and extravascular compartments is defined by Starling's law of the capillary,[22] which states that the transcapillary movement of fluid is the consequence of an imbalance between opposing filtrative and absorptive forces. This principle was applied to the lungs by Levine et al.,[23] who showed that the

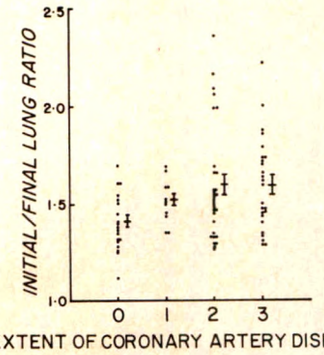


FIGURE 3. Comparison of the initial/final lung ratios in 86 patients graded according to the extent of coronary artery disease (greater than 50 percent stenosis of luminal diameter). 0 = no significant disease; 1, 2 and 3 = one, two and three vessel disease, respectively.

accumulation of water in lung tissue is directly related to intravascular forces with only a small contribution stemming from pericapillary forces. The consequent increase in hydrostatic pressure during left ventricular failure will drive fluid and thallium from the capillary to the interstitium. In our study, the experimental model that most closely approximated this situation was balloon obstruction of the left atrium. The animal data suggest that as the mean left atrial pressure increases, so does lung extraction of thallium-201. The results derived from our measurements indicate that hydrostatic pressure plays a role in the transcapillary migration of thallium-201 and that an increase in mean pulmonary arterial pressure is associated with a rise in the extraction fraction.

Geometric factors such as body shape, breast uptake, or attenuation might contribute to some differences among patients. Geometric factors alone could not have accounted for the quantitatively demonstrated changes in retained lung thallium activity in individual patients from the initial to the delayed studies. Another factor, the effect of intrinsic pulmonary conditions such as chronic inflammatory disease and chronic obstructive

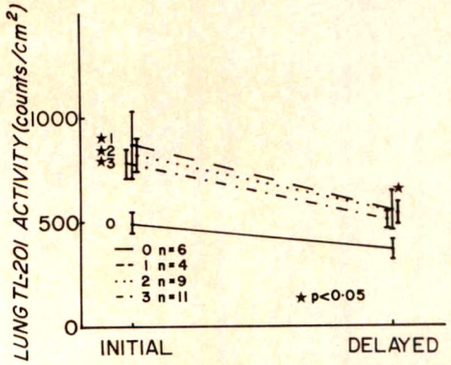


FIGURE 4. Graph showing initial and final lung activity expressed as counts/cm^2 compared with the extent of coronary artery disease (grading score as in Figure 3). **Stars** denote p value for the different groups in comparison with the group with no vessel disease.

pulmonary disease on lung uptake of thallium, is not known and cannot be derived from this study.

Clinical implications: Our data indicate that increased thallium accumulation occurs in the presence of a prolonged transit time through the lungs or of increased left atrial pressure. This finding is clearly not specific for patients with coronary artery disease, and any cause of increased left atrial pressure or prolonged pulmonary transit time such as valvular heart disease or cardiomyopathy may alter lung uptake of thallium. The significance of this observation is that lung uptake in the initial images of a thallium stress study should alert the observer to an underlying impairment of left ventricular function.

Acknowledgment

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Effect of Selective Coronary Arteriography on Left Ventricular Volumes and Ejection Fraction in Man

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This study was performed to assess the influence of selective coronary arteriography on left ventricular volumes and ejection fraction in man. In 30 patients with assorted cardiac diseases, left ventricular end-diastolic and end-systolic volumes and ejection fraction were quantitated immediately before and after selective coronary arteriography. In 19 patients (Group A), contrast left ventriculography was performed immediately before and after selective coronary arteriography. In the remaining 11 patients (Group B), multigated equilibrium blood pool imaging was performed just before and after coronary arteriography. In both groups, mean systemic arterial pressure and heart rate did not change from just before the first to immediately before the second assessment of left ventricular volumes and ejection fraction, but left ventricular end-diastolic pressure increased. End-diastolic and end-systolic volume indexes, and ejection fraction did not change from just before to immediately after selective coronary arteriography. Therefore, selective coronary arteriography (1) consistently causes an increase in left ventricular end-diastolic pressure but (2) exerts no effect on left ventricular volumes and ejection fraction, even in patients with severely compromised left ventricular function.

Previous studies in both experimental animals and human beings have shown that contrast left ventriculography and selective coronary arteriography are associated with complex changes in ventricular function and circulatory hemodynamics. The rapid injection of a large bolus dose of contrast material into the left ventricle has been reported to induce a transient increase in cardiac output,[1,2] plasma osmolality[3,4] and circulating blood volume[1,4]; an increase in left ventricular end-diastolic,[2,5–7] left atrial and pulmonary arterial pressures[5]; as well as a temporary depression of left ventricular performance.[5,6] Similarly, selective coronary arteriography has been shown to cause a brief increase in left ventricular end-diastolic pressure[8,9] and a transient reduction of ventricular performance.[10–12] These effects of radiographic contrast material on left ventricular function have led to the general recommendation that left ventriculography be performed before selective coronary arteriography[13,14] to ensure that left ventricular function is assessed correctly.

In most cardiac catheterization laboratories, left ventricular volumes and ejection fraction are utilized in conjunction with end-diastolic pressure to assess left ventricular function. This study was performed to determine the effect of selective coronary arteriography on these variables.

Methods

Procedure: In 30 patients selective coronary arteriography was immediately preceded and followed by contrast left ventriculography (Group A, 19 patients) or equilibrium gated blood pool imaging (Group B, 11 patients). Coronary arteriography was performed with the Judkins technique in all patients. Just before each assessment of left ventricular volumes and ejection fraction, systemic arterial pressure (phasic and mean) and left ventricular pressure (systolic and end-diastolic) were recorded. Left ventricular end-diastolic pressure was mea-

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sured coincident with the peak of the electrocardiographic R wave; in each subject 10 consecutive beats were averaged. After the initial assessment of left ventricular function, 4 to 7 selective injections into the left coronary artery and 1 to 3 selective injections into the right coronary artery were performed. Sublingual nitroglycerin was not administered during coronary arteriography. Immediately after the final selective injection into the right coronary artery, arterial and left ventricular pressures were recorded, after which left ventricular volumes and ejection fraction again were assessed.

Group A (19 patients): assessment of left ventricular volumes and ejection fraction with contrast ventriculography: Single plane left ventriculograms were performed in the 30° right anterior oblique projection in 19 patients both immediately before and immediately after selective coronary arteriography. All ventriculograms were performed with a pigtail catheter. They were filmed at 60 frames/s on Kodak CFA 1530 35 mm film. For each ventriculogram, Renografin 76® was injected at 13 to 15 ml/s for 4 seconds (total, 52 to 60 ml). Just before the first ventriculogram, a grid with multiple 1 cm^2 sections was positioned at the level of the mid left ventricle under lateral fluoroscopic control and was recorded on film. Both tube height and patient angulation were noted and duplicated during the second ventriculogram.

The 19 patients consisted of 10 women and 9 men; the average age was 43.4 years (range 20 to 59). Coronary artery disease (at least 70 percent narrowing of luminal diameter) was present in 10 patients (single vessel disease in 4, double vessel disease in 2 and triple vessel disease in 4). Three patients had congestive cardiomyopathy, two had an atrial septal defect and the remaining four had no demonstrable cardiac disease on catheterization, although they complained of occasional chest pain. In these 19 patients, the time that elapsed between the first and second ventriculograms averaged 35.6 ± 9.4 minutes (mean ± standard deviation) (range 19 to 55), and the time between the final right coronary arterial injection and the second ventriculogram averaged 5.0 ± 1.2 minutes (range 3 to 8).

After the catheterization procedure, the ventriculograms were viewed on a Vanguard XR 35 projector, and the end-diastolic and end-systolic silhouettes were isolated and traced and their areas determined by two independent observers using manually performed planimetry. The ventricular volumes were calculated with use of the standard area-length method,[15] and the data modified using the Kennedy regression equation.[16] The values obtained by the two observers were averaged.

Group B (11 patients): assessment of left ventricular volumes and ejection fraction with multigated equilibrium blood pool imaging: Approximately 1 hour before selective coronary arteriography, in vivo labeling of red blood cells was accomplished by the administration of unlabeled stannous pyrophosphate (Pyrotech®, Squibb Pharmaceutical Company), followed 15 to 30 minutes later by 30 millicuries of technetium-99m sodium pertechnetate, as previously described.[17–19] The data collection was performed with a portable gamma camera computer system (Ohio Nuclear Series 550) utilizing an all-purpose parallel hole collimator. After a period of at least 10 minutes (to allow for in vivo red cell binding and equilibration within the blood pool), the activity of a peripheral venous blood sample, 3 ml in size, was determined. Then, just before and immediately after selective coronary arteriography, equilibrium gated blood pool scintigrams were obtained in a 35° left anterior oblique projection with 15° of caudad angulation; the exact angle of obliquity was always readjusted to allow the clearest separation between the left and right ventricles while minimizing the thickness of the interventricular septum. All studies were gated for 28 frames/cardiac cycle and collected for a preselected number of cardiac cycles. Each equilibrium blood pool scintigram was acquired over a period of 3 to 5 minutes, resulting in approximately 250,000 counts/frame of the study.

The group consisted of 5 women and 6 men; the average age was 54.2 years (range 25 to 76). Coronary artery disease as defined earlier, was present in eight patients (single vessel disease in two, double vessel disease in one and triple vessel disease in five). One patient had congestive cardiomyopathy, and the remaining two patients had no demonstrable cardiac disease on cardiac catheterization. In these 11 patients, the elapsed time between the first and second gated blood pool scintigrams averaged 39.8 ± 7.5 minutes (range 25 to 52), and the time between the final right coronary arterial injection and the second scintigram averaged 6.1 ± 1.2 minutes (range 4 to 8).

After the catheterization procedure, the end-diastolic and end-systolic frames were isolated from the sequence of images. Background subtraction was performed with a linear interpolated background subtraction technique, as described previously.[20] The end-diastolic and end-systolic perimeters were outlined and the total number of counts within each perimeter determined. Left ventricular volumes and ejection fraction were calculated by two independent observers using the method previously described,[19] and the values obtained by the two observers were averaged.

Statistical analysis: For each assessment of left ventricular volumes and ejection fraction in each patient, values for end-diastolic volume index, end-systolic volume index, ejection fraction, mean systemic arterial pressure, heart rate and left ventricular end-diastolic pressure were obtained. For each of these variables, a mean and standard deviation of the mean were determined for the first and second assessments. The values during the first assessment were compared with those during the second assessment within the same group of patients using the paired t test. A probability (p) value of 0.05 or less was considered significant.

Results

Effect of selective coronary arteriography on systemic arterial pressure, heart rate and left ventricular end-diastolic pressure: In Group A (contrast ventriculography before and after selective coronary arteriography), mean systemic arterial pressure did not change from just before the first to immediately before the second ventriculogram (98.1 ± 14.0 and 96.4 ± 13.7 mm Hg, respectively; difference not significant [NS]). Similarly, heart rate was unchanged from the first to the second ventriculogram (74.8 ± 15.0 and 75.7 ± 13.6 beats/min, respectively; NS). However, mean left ventricular end-diastolic pressure increased significantly, from 12.9 ± 6.4 mm Hg before the first ventriculogram to 17.2 ± 6.9 mm Hg before the second ($p < 0.0005$) (Fig. 1).

In Group B (equilibrium gated blood pool imaging before and after selective coronary arteriography), the alterations in systemic arterial pressure, heart rate and left ventricular end-diastolic pressure were similar. Specifically, mean systemic arterial pressure did not change from immediately before the first to just before the second gated blood pool scintigram (87.9 ± 9.3 and 88.9 ± 11.9 mm Hg, respectively; NS), and heart rate was unchanged from the first to the second blood pool scintigram (78.3 ± 12.6 and 78.9 ± 12.9 beats/min, respectively; NS). As in Group A, left ventricular end-

diastolic pressure increased significantly, from 14.1 ± 8.1 mm Hg before the first gated scintigram to 17.5 ± 7.4 mm Hg before the second ($p < 0.025$) (Fig. 1).

Effect of selective coronary arteriography on left ventricular volumes and ejection fraction: In Group A (contrast ventriculography before and after selective coronary arteriography), end-diastolic volume index, end-systolic volume index and ejection fraction did not differ from the first to the second ventriculogram. Specifically, end-diastolic volume index averaged 78.7 ± 29.8 ml during the first ventriculogram and 77.3 ± 26.8 ml during the second (NS); end-systolic volume index was 42.5 ± 27.1 ml during the first ventriculogram and 41.5 ± 26.0 ml during the second (NS); ejection fraction averaged 0.48 ± 0.15 during both the first and second ventriculograms (NS) (Fig. 2). The findings were similar in Group B (equilibrium gated blood pool imaging before and after selective coronary arteriography). The mean end-diastolic volume index was 85.1 ± 34.4 and 84.5 ± 33.4 ml during the first and second blood pool scintigrams, respectively (NS) and end-systolic volume index averaged 49.7 ± 34.2 ml during the first scintigram and 49.3 ± 33.2 ml during the second (NS); ejection fraction was 0.50 ± 0.20 with the first gated image and 0.50 ± 0.20 during the second (NS) (Fig. 2). Thus, values for end-diastolic volume index, end-systolic volume index, and ejection fraction immediately after selective coronary arteriography were not significantly different from those immediately before selective coronary arteriography, irrespective of the technique used to measure these variables (contrast ventriculography or equilibrium gated blood pool imaging).

Discussion

Many studies have demonstrated that the intravascular administration of radiographic contrast material causes substantial alterations of cardiac output,[1,2] intracardiac pressures[2,5–7] and left ventricular performance.[5,6] Whereas most of these studies have evaluated the effects of rapid, large bolus injections of contrast material, such as those used in left ventriculography, relatively few studies have attempted to examine the influence of selective coronary arteriography on left ventricular function. Therefore, this study was per-

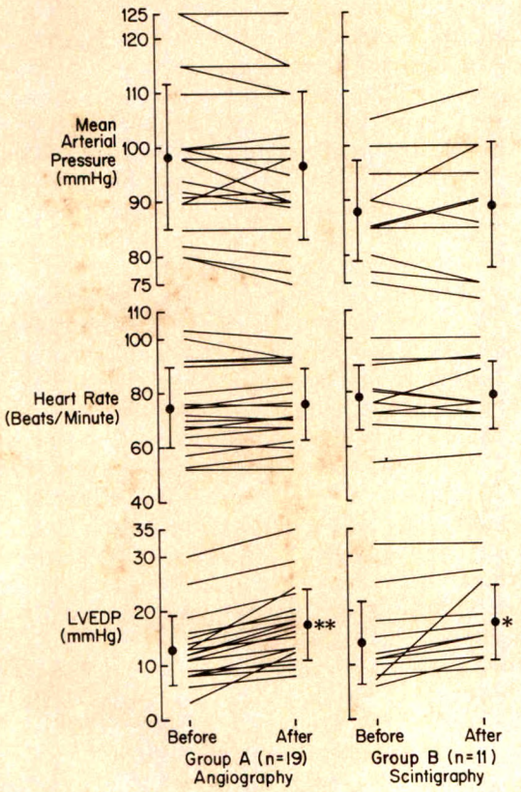


FIGURE 1. Values for mean systemic arterial pressure (**top**), heart rate (**middle**), and left ventricular end-diastolic pressure (LVEDP) (**bottom**) both before and after selective coronary arteriography in 19 patients who underwent contrast ventriculography (Group A) and in 11 patients who underwent equilibrium gated blood pool imaging (Group B) for quantitation of left ventricular volumes and ejection fraction. Each line represents the values from one patient, and the mean values ± standard deviation are depicted to the left and right of each group of lines. In both groups mean systemic arterial pressure and heart rate did not change significantly from just before the first to immediately before the second assessment. In contrast, left ventricular end-diastolic pressure increased significantly in both groups. *$p < 0.025$; **$p < 0.0005$.

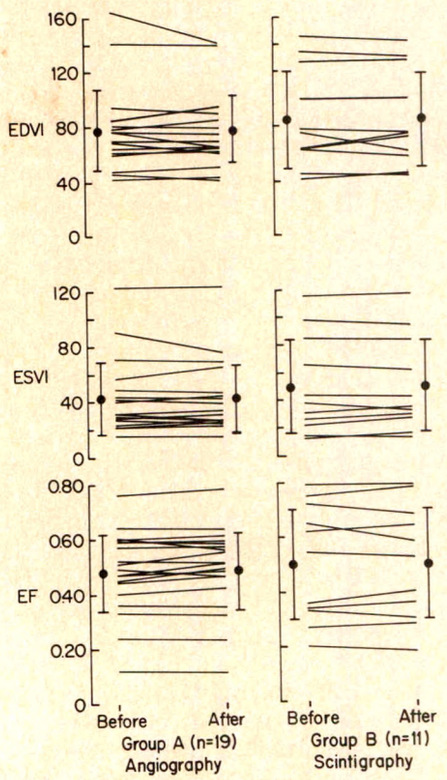


FIGURE 2. Values for end-diastolic volume index (EDVI) (**top**) end-systolic volume index (ESVI) (**middle**), and ejection fraction (EF) (**bottom**) both before and after selective coronary arteriography in the 19 patients who underwent contrast ventriculography and in the 11 who underwent equilibrium gated blood pool imaging. Conventions are as in Figure 1. In both groups, there was no significant change in the three variables from just before to just after selective coronary arteriography. Even in the patients with an extremely poor ejection fraction during the first assessment, coronary arteriography did not adversely affect ejection fraction.

formed to assess the effect of selective coronary arteriography on left ventricular volumes and ejection fraction in man.

Effect of contrast ventriculography: The rapid intravascular administration of a large quantity of contrast material (0.6 to 1.0 ml/kg body weight) has been demonstrated to exert a profound effect on cardiac output, intracardiac pressures and ventricular performance. Within the 1st minute after such an intravascular injection, cardiac output increases substantially (by as much as 50 percent),[1,2] systemic arterial pressure decreases (by as much as 20 to 30 percent),[2] heart rate increases by 10 to 15 percent[2] and pulmonary arterial, left atrial and left ventricular end-diastolic pressures increase substantially.[2,5–7] Simultaneously, myocardial "contractility" decreases.[5,6,10] These variables gradually return to baseline over the ensuing 15 to 20 minutes. Specifically, systemic arterial pressure and heart rate return to the baseline values within 3 to 4 minutes,[2] whereas cardiac output and left ventricular end-diastolic pressure revert to their baseline values within 15 to 20 minutes.[1,5] Therefore, by 15 to 20 minutes after a large intravascular injection of radiographic contrast material, no alterations in cardiac output or intracardiac pressures are demonstrable.

Effect of coronary arteriography: In contradistinction to a large intravascular injection of radiographic contrast material, selective coronary arteriography involves the repetitive injection of contrast medium into the coronary arteries in relatively small amounts (5 to 10 ml/injection). The left coronary artery usually receives three to six injections over a period of 3 to 10 minutes, and the right coronary artery receives two to three injections over 2 to 4 minutes. Although selective coronary arteriography causes a transient reduction in systemic arterial pressure and heart rate, these variables generally return to baseline within 15 to 30 seconds. Cardiac output and stroke volume are not altered by selective coronary arteriography.[8] However, like large intravascular injections of contrast material, selective coronary arteriography causes an increase in left ventricular end-diastolic pressure. In fact, some investigators[9] have attempted to utilize the magnitude of this increase in left ventricular end-diastolic pressure after selective coronary arteriography as an index of the severity of the cardiac disease. Our study demonstrates clearly that left ventricular end-diastolic pressure is increased modestly but significantly by selective coronary arteriography. Specifically, in our patients end-diastolic pressure increased from 13.3 ± 6.8 mm Hg before coronary arteriography to 17.3 ± 6.9 mm Hg immediately after coronary arteriography.

There have been some previous attempts to determine the effect of selective coronary arteriography on left ventricular volumes and ejection fraction. In dogs, coronary arteriography caused a modest increase in left ventricular end-diastolic and end-systolic volumes but no change in ejection fraction.[8] In human beings, contrast left ventriculography was performed immediately before and after selective coronary arteriography, and values for left ventricular volumes and ejection fraction during the second ventriculogram were compared with those during the first; no significant alterations occurred in end-diastolic or end-systolic volume or in ejection fraction.[21] Our study also demonstrates that left ventricular volumes and ejection fraction assessed angiographically are not altered by selective coronary arteriography. Specifically, in our Group A, left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured with contrast left ventriculography both before and after selective coronary arteriography. Because the second ventriculogram was performed an average of 35.6 ± 9.4 minutes (range 19 to 55) after the initial ventriculogram, the second ventriculogram probably was not influenced by the first bolus injection of contrast material. When values for ventricular volumes and ejection fraction during the second ventriculogram were compared with those during the first ventriculogram, there was no significant difference (Fig. 2). Even in patients whose ejection fraction was substantially depressed, selective coronary arteriography did not influence left ventricular volumes or ejection fraction.

Role of equilibrium gated blood pool imaging: Previous studies[1,2,5] have shown that a large bolus injection of contrast material exerts a demonstrable hemodynamic effect for 15 to 20 minutes. In the present study, because the second contrast ventriculogram was performed 35.6 ± 9.4 minutes after the first ventriculogram, it is unlikely that ventricular function at the time of the second ventriculogram was affected by the first. However, to eliminate any possible influence of a residual effect, we performed equilibrium gated blood pool imaging immediately before and after selective coronary arteriography in 11 patients (Group B). Like contrast ventriculography, equilibrium gated blood pool imaging allows the quantitation of left ventricular volumes and ejection fraction[19] but, unlike ventriculography, it exerts no discernible effect on hemodynamic variables or ventricular function. Thus, performing blood pool imaging before and after selective coronary arteriography allowed us to assess the effect of coronary arteriography alone on left ventricular performance without the residual effect (small though it may be) of previous contrast ventriculography. In our Group B (as in Group A), ventricular volumes and ejection fraction were not influenced by selective coronary arteriography.

Mechanisms of depressed left ventricular performance: Several studies have attempted to elucidate the mechanisms whereby radiographic contrast materials cause a transient depression of left ventricular performance. The extreme hyperosmolarity (about 1,800 milliosmoles/liter) and high sodium content (approximately 190 mEq/liter) of the commonly employed contrast materials contribute substantially to this depression.[11,22] In addition, recent studies in the anesthetized dog have shown that the intracoronary administration of radiographic contrast material causes a profound transient decline in the concentration of both total and ionized calcium within the blood perfusing the myocardium. This diminution of calcium is

associated with a concomitant brief (30 to 45 seconds) reduction in left ventricular contractile force.[12]

In our study, the second assessment of left ventricular volumes and ejection fraction was performed 5.3 ± 1.3 minutes (range 3 to 8) after the final injection into the right coronary artery. During this time period, a catheter exchange was performed, and left ventricular and systemic arterial pressures were recorded. It is conceivable that such an assessment performed within 1 to 2 minutes of selective coronary arteriography might have demonstrated a residual depressant effect of contrast material on left ventricular performance.

Implications: This study demonstrates that selective coronary arteriography does not alter left ventricular volumes or ejection fraction, even in patients with severely depressed ventricular function. However, selective coronary arteriography does affect left ventricular end-diastolic pressure. Therefore, intracardiac pressures should be measured before the injection of radiographic contrast material, but left ventricular volumes and ejection fraction can be quantitated at any time during catheterization, even after selective coronary arteriography. Patients in clinically unstable condition may tolerate injections of contrast material poorly. In such patients, it may be preferable to assess coronary arterial anatomy as quickly as possible, thus postponing an evaluation of left ventricular volumes and ejection fraction until such coronary arteriography has been completed.

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Semiautomated Method for Evaluation of Left Ventricular Regional Wall Motion in Coronary Artery Disease

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Regional left ventricular wall motion was independently assessed in 436 patients using both subjective visual inspection of ventriculograms and objective computer-determined percent change in the square root of the area between systolic and diastolic outlines. Agreement between subjective and objective techniques was greatest at the ventricular apex and least at the base and partly dependent on the number of abnormal segments present. Objective analysis of regional wall motion provides a permanent quantitative record of wall motion and shows good agreement with meticulous subjective inspection of ventriculograms. As such, it has potential as an adjunct to ventriculography.

Although various noninvasive techniques have been used to assess left ventricular function, left ventricular cineangiography remains the standard of reference in studies dealing with impairment of left ventricular performance.[1–4] The determination of ventricular volumes and ejection phase indexes from cineangiographic frames has been facilitated by the development of simple quantitative methods.[5] However, regional wall motion has proved less susceptible to quantitative analysis and is most often assessed visually. The error inherent in subjective (versus objective) readings of ventricular wall motion was clearly demonstrated by Chaitman et al.[6] In this paper we compared an objective method of wall motion analysis with subjective readings performed by experienced observers. The results of correlation of subjective with objective methods in more than 400 ventriculograms suggest that the objective technique is valuable as both (1) a check on subjective ventriculographic readings, and (2) a permanent quantitative document that may be carried in the outpatient chart in either numerical or graphic form.

Methods

Patients: The ventriculograms of 436 patients who underwent selective coronary arteriography and left ventriculography between 1972 and 1977 were reviewed. All patients had isolated coronary artery disease and complained of angina pectoris.

Ventriculography and subjective analysis: More than 90 percent of the angiographic studies were performed percutaneously from the femoral artery; the remainder were performed from the brachial artery using a cutdown in the arm. The left ventriculograms were exposed on 35 mm film at 60 frames/s in the right anterior oblique projection using a Philips 9 inch (22.9 cm) cesium iodide image intensifier system (Philips Medical Systems, Inc., Shelton, Connecticut). Forty-five cc of 76 percent meglumine diatrizoate was injected into the left ventricle in 3 seconds using a power injector. Only frames separated from ectopic beats by at least two cardiac cycles were analyzed. All films were of excellent quality. The ventriculograms were divided into five left ventricular areas (Fig. 1) and each area was reviewed by three experienced physicians. A consensus was reached when differences existed in the interpretation of this material; such differences were rare and minor in nature. Ejection fraction was calculated from a standard formula.

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The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department.

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Objective analysis: Regional left ventricular wall motion was analyzed by a method we[7] previously reported. Each left ventriculogram was manually traced onto a Talos XY digitizer (Talos, Inc., Scottsdale, Arizona). The magnification correction grid and end-diastolic and end-systolic frames were digitized. The ventricular ejection fraction was computed using a desk-top calculator (Tektronix 4051) interfaced with the digitizer. The calculator was programmed to check and correct for rotation and translation of the left ventricle during the cardiac cycle by rotating the systolic outline about the points of intersection of the long axes or, when these were parallel, shifting the systolic outline perpendicularly until the long axes overlapped. Segmental wall motion was analyzed by dividing the ventricular area into 12 pie-shaped sections originating from the center of the long axis at end-diastole (Fig. 2). This was accomplished by transforming the Cartesian coordinates characterizing the diastolic and systolic outlines into polar coordinates[7,8] originating from the center, which was assumed to be at the mid point of the diastolic long axis. The diastolic (A_{Di}) and systolic (A_{Si}) areas of each segment (i) were calculated. The motion of each pie-shaped segment was expressed as the difference between the square roots of A_{Di} and A_{Si} divided by the square root of A_{Di}, or percent change in the square root of area between diastole and systole for any i^{th} segment ($\%\Delta\sqrt{A_i}$).

Data analysis: Subjective analysis of left ventricular wall motion area was compared blindly with computer-assisted wall motion segmental analysis. This was accomplished by deletion of computer segments 1 and 12 (Fig. 2) and comparison of subjectively analyzed left ventricular areas 1, 2, 3, 4 and 5 (Fig. 1) with the computer-analyzed segments 2 to 3, 4 to 5, 6 to 7, 8 to 9 and 10 to 11 (Fig. 2). Any computer-analyzed segmental pair was classified as abnormal if either of the two segments composing a pair showed a value for $\%\Delta\sqrt{A}$ below the mean value −1.5 standard deviations derived from ventriculograms of 48 normal adults[7] (Fig. 3). The standard deviation of 1.5 was chosen because (1) it resulted in approximately the same number of abnormal interpretations as did the meticulous subjective technique; (2) the occurrence of hyperkinesia tended to increase the mean scores of the group as a whole, permitting the "minus standard deviation" number to be less negative yet still pick up abnormal readings; and (3) the false-positive reading below mean −1.5 standard deviations in the normal population[7] was 4 percent for 5 of the 12 segments, 2 percent for 3 segments, and 0 percent for the remaining 4 segments (Fig. 2).

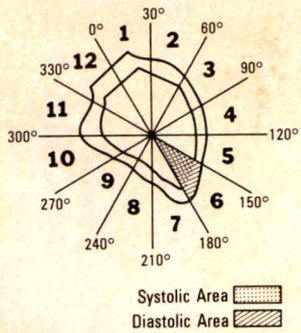


FIGURE 2. Objective, computer-assisted ventriculogram analysis: Systolic and diastolic outlines are partitioned into 12 equal segments, 0° falling at the mid point of the aortic valve; segments 30° to 90°, 90° to 150°, 150° to 210°, 210° to 270° and 270° to 330° correspond to areas 1, 2, 3, 4 and 5, respectively, in Figure 1.

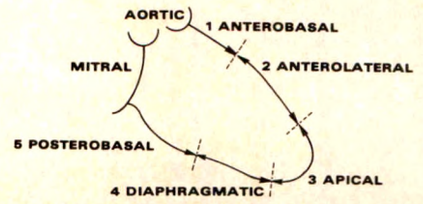


FIGURE 1. Subjective ventriculographic analysis. Systolic and diastolic outlines are visually partitioned into five areas, each assessed as normal or abnormal.

For each of 436 patients, subjective readings (normal or abnormal) for five areas were superimposed on five paired segmental, objective computer-analyzed readings. Each normal-normal or abnormal-abnormal concordant result was counted as a scored point. Perfect subjective-objective correlation in one patient would therefore yield a maximum of five agreement points. It was obvious to us that occasionally an abnormal left ventricular area might be read as occurring in a given sector by the subjective method, whereas the computer might classify the same abnormal motion as occurring in an adjacent left ventricular sector. This would lead to two scoring errors (abnormal-normal; normal-abnormal) and would tend to obscure the fact that both cardiologist and computer responded to abnormal wall motion in one general vicinity. Nevertheless, our rigorous scoring system, with a total of five subjective-objective agreement points per patient, was followed.

The distribution of regional wall motion interpretations by subjective examiner and computer were depicted as 2 by 2 matrixes. With use of the subjective method as a standard, the sensitivity, specificity, predictive value of a positive test and predictive value of a negative test of the computer technique were determined. An instance in which the computer identified a segment as abnormal but the subjective examiner called it normal was considered false positive (FP). Conversely, a normal computer reading on a segment judged ab-

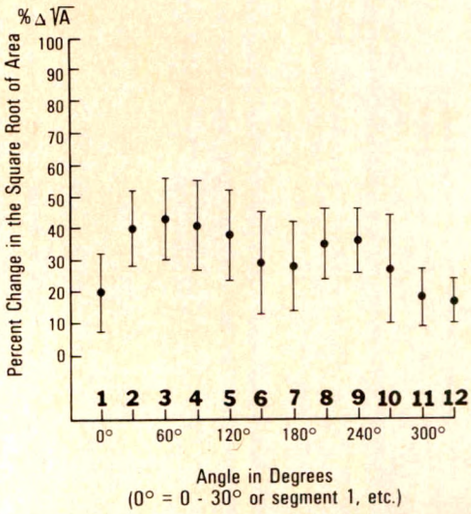


FIGURE 3. Computer-derived normal values for segmental wall motion (mean ± 1.5 standard deviations) in 48 normal adults.[7] Wall motion is expressed as percent change in the square root of the area between diastole and systole ($\%\Delta\sqrt{A}$) for each of the 12 segments shown in Figure 2.

normal by the subjective examiner was considered false negative (FN). True negative (TN) and true positive (TP) scores represented subjective-objective agreement. Sensitivity was computed as TP/(TP + FN), specificity as TN/(TN + FP), predictive value of a positive test as TP/(TP + FP) and predictive value of a negative test as TN/(TN + FN).

Ejection fractions determined with standard planimetric techniques were correlated with computer-determined values for all patients. The r value was estimated by calculating the Pearson product-moment correlation coefficient.

Results

Ejection fraction obtained with standard planimetric techniques correlated highly (r = 0.94) with ejection fraction obtained with the computer method. This value was statistically significant ($p < 0.001$).

Regional wall motion: Table I shows the distribution of regional wall motion interpretations in 436 patients. Sensitivity, specificity, predictive value of a positive test and predictive value of a negative test of the computer method compared with values obtained with subjective readings are shown together with an agreement score.

These data can be summarized in the following fashion: (1) Normal areas predominated in all ventricular regions, disproportionately so in area 1. (2) Concordance was weakest at the ventricular base and strongest at the apex. (3) The high percent of normal-normal agreement in area 1 reflects the small number of abnormal segments detected in this area. The predictive value of an abnormal finding with the computer method was low (12.1 percent). (4) When the subjective method was used as a standard, computer analysis of regional wall motion had fair sensitivity (62.2 percent overall, with the least sensitivity in the diaphragmatic area) but had very high specificity (89.4 percent overall). (5) Total subjective-computer agreement was high overall (83 percent concordance).

The possibility that the number of abnormal areas affected concordance was examined. Table IIA shows the number of patients with 0, 1, 2, 3, 4 or 5 abnormal areas by subjective, computer or combined techniques, and Table IIB shows for each group an average agreement score.

This information is summarized as follows: (1) Generally there were modest differences between methods in the number of patients with a given number of abnormal areas. (2) There was a descending order of frequency from no abnormal areas to five abnormal areas, although abnormalities in paired areas may occur slightly more often than abnormalities in a single area. (3) Concordance appeared to be influenced by the number of abnormal areas. Agreement was inversely related to the number of abnormal areas until the largest number (five) was reached, at which point agreement increased.

Discussion

Subjective versus objective computer analysis of ventricular wall motion: We were able to characterize left ventricular wall motion adequately with use of

TABLE I

Distribution, Sensitivity and Specificity of Regional Wall Motion Findings: Data Derived by Comparing Computer-Assisted Interpretation With Subjective Observer Interpretation Used as Reference

Subjective Examiner:		Computer: Normal			Computer: Abnormal		where n = 436 patients, 2180 segments
Normal		NN	NA	or	TN	FP	
Abnormal		AN	AA		FN	TP	

	Computer Distribution (Number of Segments)		Percent Distribution		Sensitivity (%) TP / TP + FN	Specificity (%) TN / TN + FP	Percent Agreement (normal-normal % plus abnormal-abnormal %)	Predictive Value of Positive Test (%) TP / TP + FP	Predictive Value of Negative Test (%) TN / TN + FN
Subjective areas 1–5	N 1472	174	67.5	8.0	62.0	89.4	82.7	65.5	87.9
	A 202	332	9.3	15.2					
1. Antero-basal area	N 402	29	92.2	6.7	81.0	93.2	93.1	11.8	99.8
	A 1	4	0.2	0.9					
2. Antero-lateral area	N 264	31	60.5	7.1	59.6	89.5	79.8	73.1	82.2
	A 57	84	13.1	19.3					
3. Apical area	N 260	36	59.6	8.3	74.1	87.8	83.4	74.1	87.8
	A 36	104	8.3	23.8					
4. Diaphragmatic area	N 276	9	63.3	2.1	49.7	96.8	80.5	89.1	78.4
	A 76	75	17.4	17.2					
5. Posterobasal area	N 270	69	61.9	15.8	67.3	79.7	76.9	48.7	89.5
	A 32	65	7.3	15.0					

A = abnormal; FN = false negative; FP = false positive; N = normal; TN = true negative; TP = true positive.

subjective and objective assessments around the left ventricular perimeter. There was generally good agreement between cardiologist and computer on normal and abnormal motion with the computer programmed for confidence limits (1.5 standard deviations) based on studies in 48 healthy adults.[7] Computer-determined ejection fraction correlated highly with the value determined with planimetry. Agreement between subjective and objective methods was not equal in all areas. The 93 percent agreement reported for area 1 (anterobasal) was partly a consequence of the small number of abnormal segments (34) detected with either method; thus, both computer (92 percent) and cardiologist (99 percent) were likely to judge area 1 normal in most patients, thereby producing nearly perfect agreement.

In areas two through five (anterolateral, apex, diaphragmatic and posterobasal) the majority of abnormal areas were detected. The greatest frequency of abnormal left ventricular areas and the greatest subjective-objective concordance occurred at the ventricular apex (83 percent), a highly visible and well defined myocardial region. On either side of the apex (anterolateral and diaphragmatic areas) agreement was equal (80 percent). Subjective-objective agreement decreased to 78 percent in the less clearly defined posterobasal area.

When a meticulous subjective analysis of ventricular wall motion is used as the "gold standard," the sensitivity and specificity of the more objective computer technique can be examined. We found sensitivity in various regions to range from 50 to 80 percent. However, specificity was considerably higher (about 90 percent overall). It was also apparent that the number of abnormal segments influenced subjective computer concordance: The highest values were obtained for patients with no, one or five abnormal segments.

Advantages of computer-assisted analysis of wall motion: Chaitman et al.[6] have previously attempted to compare objective and subjective analysis of left ventricular angiograms. These investigators found wide variability (nearly 30 percent) in regional wall motion assessments between a subjective observer and an objective area-chord technique. Better concordance occurred between subjective observers (24 percent), between observers using an objective technique (8 percent) and between the same observer on different occasions (1 percent). Obviously, in clinical studies the information of greatest scientific value is that which can be obtained not only by one observer but also by many observers in an independent, reproducible way. Moreover, the less judgment or skill requisite to interpret such information, the more shareable it is with nonspecialists. We believe that computer-assisted analysis of regional left ventricular wall motion provides an objective, highly transferable record that compares favorably with the subjective technique now in use; this analysis is more descriptive than a subjective observer's dictation, easier to find and use than the cine films from which the analysis was taken, and more shareable with nonspecialists than the standard ventriculographic report.

This is not the first description of a semiautomated technique for evaluation of left ventricular regional wall motion.[8,9] However, it does analyze an unusually large sample size using percent change in the square root of the area between systole and diastole as an index of segmental activity. The similar area technique has previously been validated as superior to chord and radius methods for left ventricular wall motion analysis.[4] By taking the square root of radially distributed segments, we provide the additional benefit of obtaining an average measure of radius.

Implications: On occasion the computer has detected wall motion abnormalities that were previously missed on subjective visual analysis and later confirmed on reexamination of the angiographic films.[10] We did not

TABLE IIA

Number of Patients (%) With 0, 1, 2, 3, 4 or 5 Abnormal Areas Detected With Various Methods

	Abnormal Areas					
	0	1	2	3	4	5
a. By subjective examiner	184 (42.2)	81 (18.6)	98 (22.5)	41 (9.4)	29 (6.7)	3 (0.7)
b. By computer technique	185 (42.4)	98 (22.5)	90 (20.6)	37 (8.5)	17 (3.9)	9 (2.1)
c. Any segment abnormal by either a or b	126 (28.9)	92 (21.1)	106 (24.3)	62 (14.2)	31 (7.1)	19 (4.4)

TABLE IIB

Agreement Scores in Patients With 0, 1, 2, 3, 4 or 5 Abnormal Areas (scores are normal/normal + abnormal/abnormal relations divided by number of patients)

	Abnormal Areas					
	0	1	2	3	4	5
a. By subjective examiner	4.60	3.90	3.96	3.39	3.44	4.33
b. By computer technique	4.53	3.81	4.00	3.67	3.53	3.89
c. Any segment abnormal by either a or b	5.00	4.16	3.91	3.39	3.29	3.21

reevaluate our angiograms in cases of false positive or false negative results to determine which method was "wrong." Had we used the objective technique rather than visual inspection as the "gold standard," the respective values for sensitivity and specificity and the predictive values of positive and negative tests would have merely been reversed. Our findings do not resolve whether the computer or the subjective technique is more correct. Our study was designed not to answer this question but, rather, to examine objective regional wall motion analysis in the light of current practice (subjective analysis) so that differences may be noted.

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High Speed Rotating Scanner for Transesophageal Cross-Sectional Echocardiography

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In conventional cross-sectional echocardiography, the configuration of the chest or the presence of excessive chest wall tissue or air-containing lung often limits the resolution and field of view. To increase the diagnostic capability of cross-sectional echocardiography, a transesophageal ultrasonic high speed rotating scanner that can obtain cardiac images without hindrance from ribs, sternum and lung was developed. The scanner uses a single small transducer with a flexible shaft to permit easy swallowing by adults and mechanically scans ultrasonic beams within the esophagus. The small transducer in the esophagus is rotated through a full 360° at a rate of 15 to 50 cycles/s, and cardiac images obtained through the esophageal wall are displayed on a cathode ray tube in real time. The transesophageal scanning technique was evaluated in more than 50 adult patients. Aside from some slight gagging, no serious complications were encountered. In all patients, high quality images of most portions of the heart were obtained. There was little difference in the image quality among various patients.

Cross-sectional echocardiography has become an extremely important diagnostic technique. It provides, by noninvasive means, valuable information about cardiac anatomy and function not otherwise obtainable without significant risk and discomfort to the patient.[1–6] However, the configuration of the chest or the presence of excessive chest wall tissue or air-containing lung often limits the resolution and field of view in conventional cross-sectional echocardiography.[7] Consequently, it is sometimes difficult to obtain cardiac images of diagnostic quality in patients who are obese or elderly or have chronic obstructive pulmonary disease. To minimize these limitations, we[8,9] developed a transesophageal ultrasonic sector scanner that can obtain images of the heart without hindrance from the ribs, sternum or lungs. However, with this system the flexible shaft is relatively thick and the field of view is limited. In addition, the vibration the patient feels when the transducer is inserted into the esophagus may be uncomfortable. To increase the diagnostic capability of transesophageal cross-sectional echocardiography and to decrease patient discomfort during examination, we recently developed a new transesophageal ultrasonic rotating scanner that rotates a single small transducer through a full 360° in the esophagus.

Methods

Transesophageal rotating scanner: The scanner uses a single small transducer and mechanically scans ultrasonic beams within the esophagus (Fig. 1). The scanner consists of a flexible rotating shaft with a shaft housing and a drive system. A transducer and a slip-ring commutator are positioned at the tip of the flexible rotating shaft and enclosed in an oil bag (maximal diameter 15 mm). The oil bag can be filled with oil by means of an injector, and it is so elastic that its diameter varies in accordance with the amount of oil. The transducer is mounted in a 12 by 20 by 6 mm casing with rounded edges for easy esophageal passage. It has a frequency of 2.25 or 3.5 megahertz, a diameter of 10 mm and focus of 7.5 cm. The flexible rotating shaft is enclosed in an iron flexible shaft

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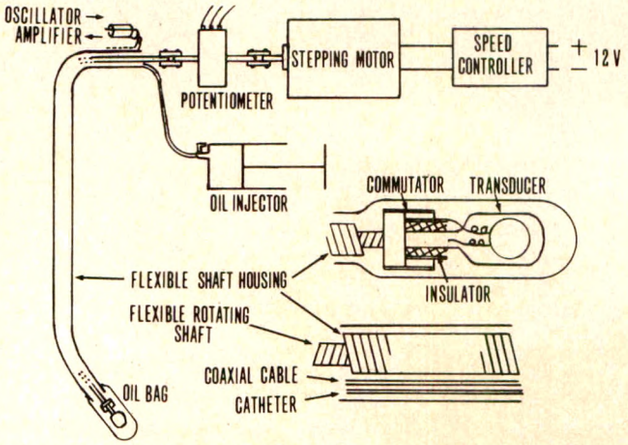


FIGURE 1. Diagrammatic illustration of the transesophageal high speed rotating scanner. A small transducer in the esophagus is rotated through a full 360° through a flexible shaft by a motor at 15 to 50 cycles/s. Although the small transducer is rotated with great speed in the patient's esophagus, no damage results because the transducer is safely enveloped in an oil bag.

housing (diameter approximately 7 mm) which is wrapped with vinyl chloride tape. The length of the shaft and housing is about 40 cm (Fig. 2). Patients can easily swallow the flexible shaft and its housing with the small transducer.

The transducer in the esophagus is rotated through a full 360° by the flexible rotating shaft and a motor at a rate of 15 to 50 cycles/s. The ultrasonic beam is swept radially so that the plane of the scan is perpendicular to the rotating shaft. The orientation of the transducer in the esophagus is detected continuously by a potentiometer installed in the drive system. The signals of the reflected echoes are transmitted through the commutator and flexible housing that contains the flexible rotating shaft and are displayed on a cathode ray tube in the B mode so that the angle of an individual scanning line is equal to the angle of the transducer at the same instant. In this way, horizontal cross-sectional images of the heart obtained through the esophageal wall are displayed on the cathode ray tube at a rate of 15 to 50 fields/s. Maximal selective pulse repetition frequency is 6.0 kilohertz. The field of view varies in depth from 10 to 17 cm according to the pulse repetition frequency. Although the ultrasonic beam is swept radially, the display angle is fixed at 180° or 260° (display angle without distortion is always 180°). In this system, only one commutator is used because the flexible rotating shaft in the flexible shaft housing acts as another commutator. Although the transducer and flexible shaft are rotated through a full 360° at high frequency, the external flexible housing remains stationary. Moreover, the enveloping oil bag prevents trauma to the esophagus (Fig. 3). Although this scanner is compatible with many commercially available ultrasonic systems, a Toshiba (model SSL-51H) transmitter-receiver was used in order to operate the scanner as a complete system.

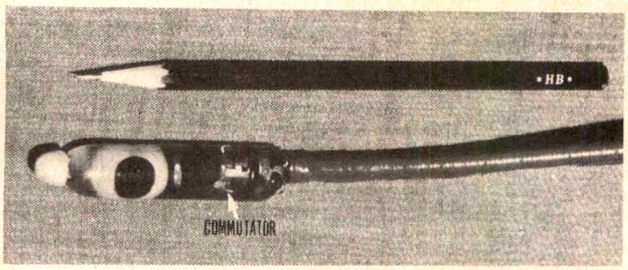


FIGURE 3. Transducer and commutator in oil bag. Sound energy is coupled to and from the transducer through the slip-ring commutator because of the full 360° rotation of the transducer.

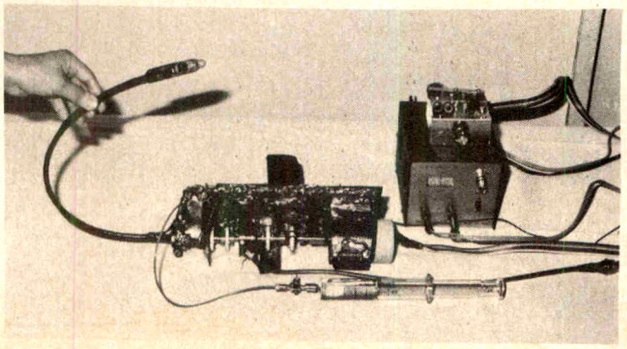


FIGURE 2. Transesophageal high speed rotating scanner.

All studies were stored on 8 or 16 mm cine film. Images were also recorded in real time on videotape.

Examination technique: This system was evaluated in 67 adult patients (average age 33.9 years, [range 17 to 73], average height 161.7 cm, average body weight 56.7 kg). Before examination, each patient usually received 0.5 mg of atropine sulfate and 10 mg of diazepam intramuscularly and 3 g of lidocaine jelly orally. The patient's throat was sprayed with 4 percent lidocaine liquid. Lidocaine jelly was applied to the oil bag and flexible housing in order to minimize discomfort and loss of contact with the esophageal wall. Insertion of the

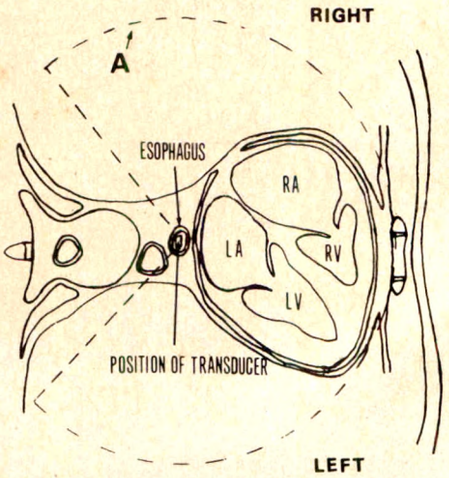


FIGURE 4. Schematic diagram showing the transducer position and typical horizontal section of the heart. The heart is viewed from the cardiac apex. The esophagus is contiguous to the heart and the heart is observed through the thin esophageal wall without hindrance from the ribs, sternum and lungs. The **dotted line** (**arrow A**) shows the area that can be observed by the transesophageal scanner. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

transducer was usually performed with subjects in the left lateral position. The transesophageal ultrasonic exmination was completed with the patients in the same position.

Usually, cardiac images were observed with the transducer inserted at a level of 30 to 40 cm. The image produced by this system is difficult to identify in comparison with that produced in conventional echocardiography. Figure 4 shows the orientation of the image produced by this system at the level of the mitral valve. The image appears as a horizontal section of the thorax viewed from the cardiac apex.

Results

Subjects usually swallowed the oil bag as easily as they would a commercially available gastrofiberscope. Gagging in various degrees was sometimes encountered until the oil bag had passed the upper part of the esophagus. Once this area had been reached, insertion was easy. Cardiac images of high quality were obtained in all subjects. At the level of the mitral valve, complete four chamber views could be observed. Unlike the procedure in conventional external echocardiography, images of the heart from base to apex were observed continuously as the transducer was withdrawn or advanced in the esophagus. Examples of transesophageal cross-sectional echocardiograms obtained in this study are shown in Figures 5 to 8.

Figure 5 shows paired diastolic and systolic scans at the level of the mitral valve in a patient with mitral stenosis. The cross section is horizontal and shows the heart as viewed from the apex. The esophagus is on the left side of the images. The left atrium is contiguous to the esophagus. The chambers are side by side and both atria and ventricles are separated by the septa and

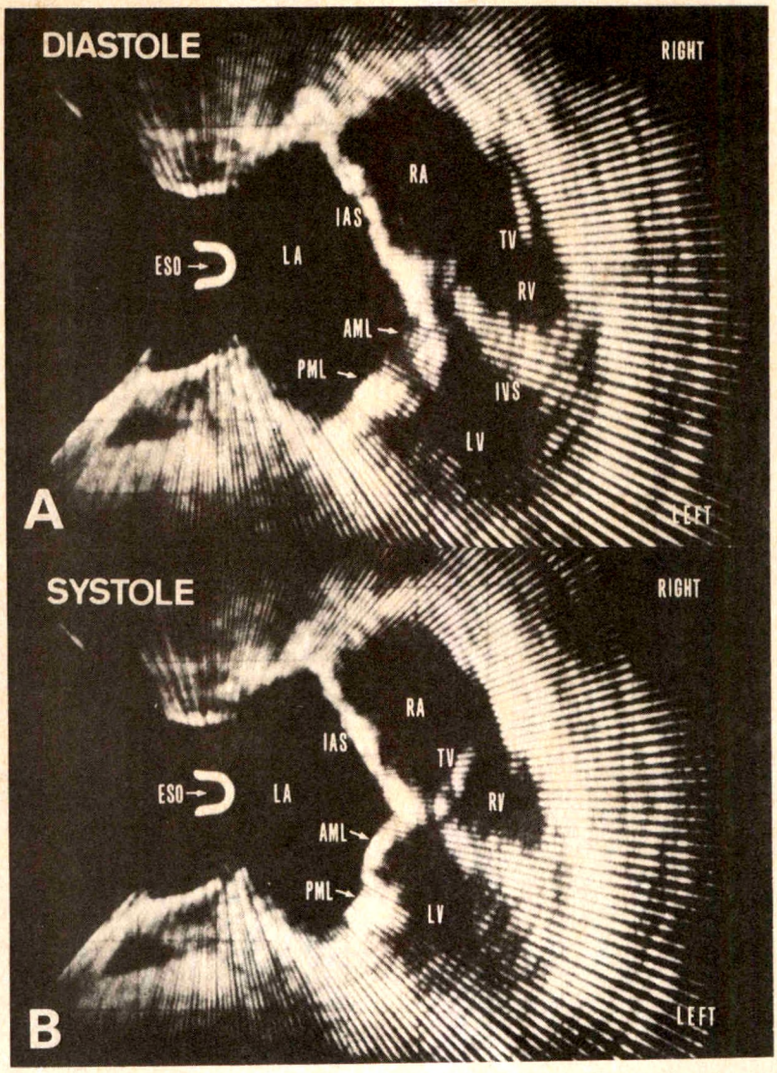


FIGURE 5. Transesophageal cross-sectional echocardiograms in a patient with mitral stenosis. The cross section is horizontal and shows the heart as viewed from the cardiac apex. **A,** a frame during diastole and **B,** a frame during systole. A stenotic mitral orifice (in **A**) is seen between the tips of the thickened mitral leaflets. The interatrial septum (IAS) is seen without dropout. AML = anterior mitral leaflet; ESO = esophagus; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PML = posterior mitral leaflet; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

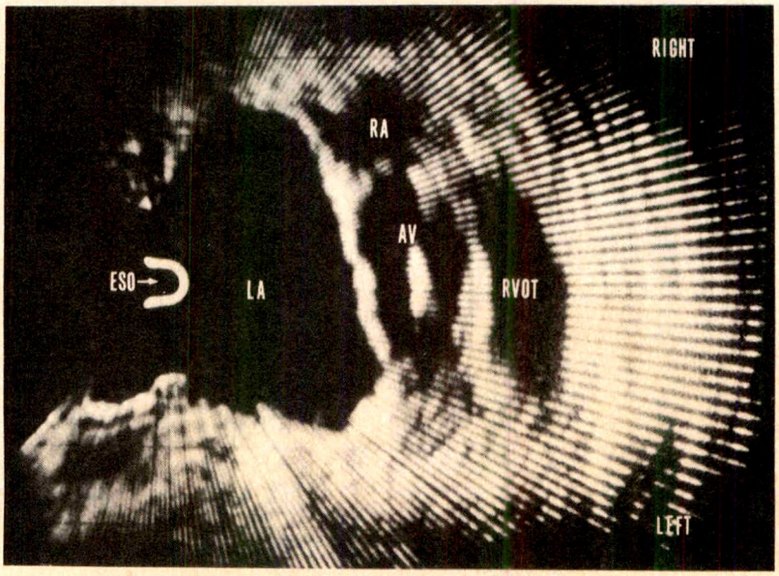


FIGURE 6. Same patient. Transesophageal horizontal cross-sectional echocardiogram at the level of the aortic valve. The heart is in diastole with the aortic valve (AV) cusps in the closed position. The left atrium (LA) is extremely enlarged. The right ventricular outflow tract (RVOT) is seen proximal to the large aorta. Unidentified abbreviations as in Figure 5.

atrioventricular valves. The left atrium is extremely enlarged. A stenotic mitral valve orifice (Fig. 5A) is seen between the tips of the thickened mitral leaflets. In contrast to the parasternal approach, the interatrial septum is seen in its entirety without dropout. On withdrawal of the transducer from this position, the aortic valve is seen (Fig. 6).

Figure 7 shows a horizontal scan at the level of the mitral valve in a patient with an ostium secondum atrial septal defect. The right atrium is enlarged. The area of echo loss in the mid portion of the septum reflects the location of the defect. Figure 8 shows a horizontal scan after repair of the defect; in this study, the interatrial septum is imaged almost continuously.

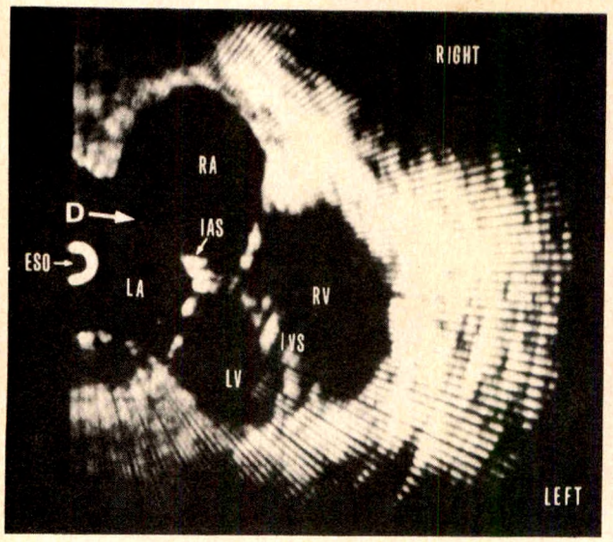


FIGURE 7. Transesophageal horizontal cross-sectional echocardiogram in a patient with an ostium secondum atrial septal defect. The large right atrium (RA) is seen. The defect (D) appears as an echo-free space in the mid portion of the interatrial septum (IAS) (**arrow**). Unidentified abbreviations as in Figure 5.

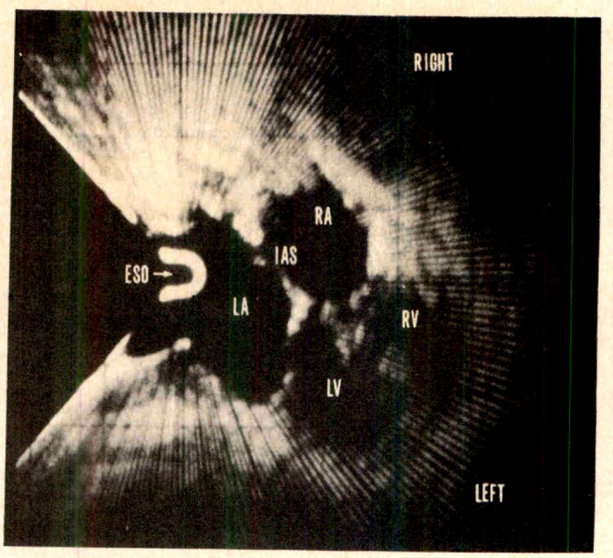


FIGURE 8. Same patient. Transesophageal cross-sectional echocardiogram after repair of the atrial septal defect. The repaired interatrial septum (IAS) is now imaged almost continuously. Abbreviations as in Figure 5.

Discussion

Ultrasonic techniques are fundamentally limited by the quality of sound transmission characteristics in a given patient. Images are impaired by chronic lung disease, abnormal chest wall configuration or age of the patient. Frazin et al.[7] reported that satisfactory M mode echoes through the chest wall cannot be obtained in about 20 percent of the patients examined. To circumvent this problem, they recorded M mode echocardiograms through the esophagus using a small transducer that patients can swallow. In contrast, we[10] developed a transesophageal pulsed Doppler echocardiographic system. The same limitations imposed by thoracic anatomy are encountered with cross-sectional echocardiographic images. Even in patients who have a normal echo window, it is impossible to observe all areas of the heart.

Transesophageal echocardiography provides a wider area for study of the heart than is available with a conventional external system. Cardiac images are observed through thin tissues in which ultrasonic absorption is very low (Fig. 4). Because there are no obstructions between the transducer and the heart except for the thin esophageal wall, there is little difference in the image quality among subjects. In clinical examinations, complete four chamber views could be obtained easily.

Insertion of the transducer and influence of the transducer rotating motion: We found that the technique for recording cross-sectional cardiac images through the esophagus presented no more problems than those encountered when observing the stomach with a commercially available gastrofiberscope. The scanning device uses a flexible shaft with a small transducer that is easily swallowed. Although the transducer is moved rapidly in the patient's esophagus, the latter is not damaged because the transducer is enclosed in an oil bag. In clinical examinations, the amount of oil in the oil bag was slightly decreased before insertion in order to facilitate insertion of the transducer into the esophagus. After insertion, oil was injected into the bag to obtain good contact between the esophageal wall and oil bag. After insertion to the 30 to 40 cm level, cardiac images of high quality were easily obtained. Apart from gagging, no serious complications were encountered. The new scanner largely overcame the problem of patient discomfort caused by transducer movement. The vibration felt by the patient during the examination decreased so remarkably that the rotation of the transducer was hardly perceived.

The electronic sector scanning system, which relies on the phased array principle, is optimal for cardiac imaging through the chest wall. However, we found this system inadequate for transesophageal imaging. One limitation is the low frequency of the transducer and another is the narrow field of view near the transducer in comparison with that of a mechanical rotating scanner. In addition, the electronic sector scanner needs numerous coaxial cables for many linearly arranged transducers. Therefore, we believe it is probably not suited for transesophageal scanning because of the proximity of the esophageal transducer to cardiac structures and because of the difficulty of swallowing a linear array of transducers with many coaxial cables.

Transesophageal cardiac images: Unlike conventional external echocardiography, our new system can record cardiac images continuously from base to apex as the transducer is being withdrawn or advanced in the esophagus. In this study the transducer position was usually identified by the mitral or tricuspid valve echo because these echoes were most easily observed in the examination. In this position, so-called four chamber views were obtained (Fig. 5), and in all patients both the mitral and tricuspid valves were observed. By withdrawing the transducer from this position, we could observe the aorta, aortic valve and right ventricular outflow tract. In comparison with the transesophageal sector scanner, the esophageal rotating scanner imaged the entire heart because the field of view was magnified. In obese or elderly patients, the subcostal and parasternal apical approaches using a conventional scanner have been used, but the quality of results was inferior to that obtained with the esophageal method.

With regard to the atrial septum, the transesophageal view is essential and cannot be replaced by other views. Because the atrial septum is more perpendicular to the incident sound energy, fewer areas of echo dropout occur. The size and shape of the atria, movement of the atrial septum, interatrial septal defects and the effect of surgery were readily evaluated with the new method (Fig. 7 and 8).

In the typical M mode esophageal echocardiographic study the target may sometimes be difficult to locate.[7] However, with our system, it is easy to obtain M mode esophageal echocardiograms of various cardiac structures. By observing B mode esophageal images, we were able to obtain a single M mode sweep of the desired target.

Potential usefulness of the method: Although our system is in an early stage of development, our initial observations suggest some future applications. One is the detection of left atrial thrombus, which is sometimes difficult with the conventional method. With the new approach, an echo of the thrombus can be detected with relative ease, because the method provides complete imaging of the entire left atrium (Fig. 6). The approach also affords demonstration of a much larger area of both ventricles than is obtained with external views (Fig. 5), thus making it possible to analyze the left and right ventricles for size and position by a side by side comparison. In addition, right and left ventricular anterior wall motion can be analyzed easily. Also, because the method affords an additional approach to imaging of the atrioventricular valves, it may be useful in studying valve disease and conditions such as mitral valve prolapse.

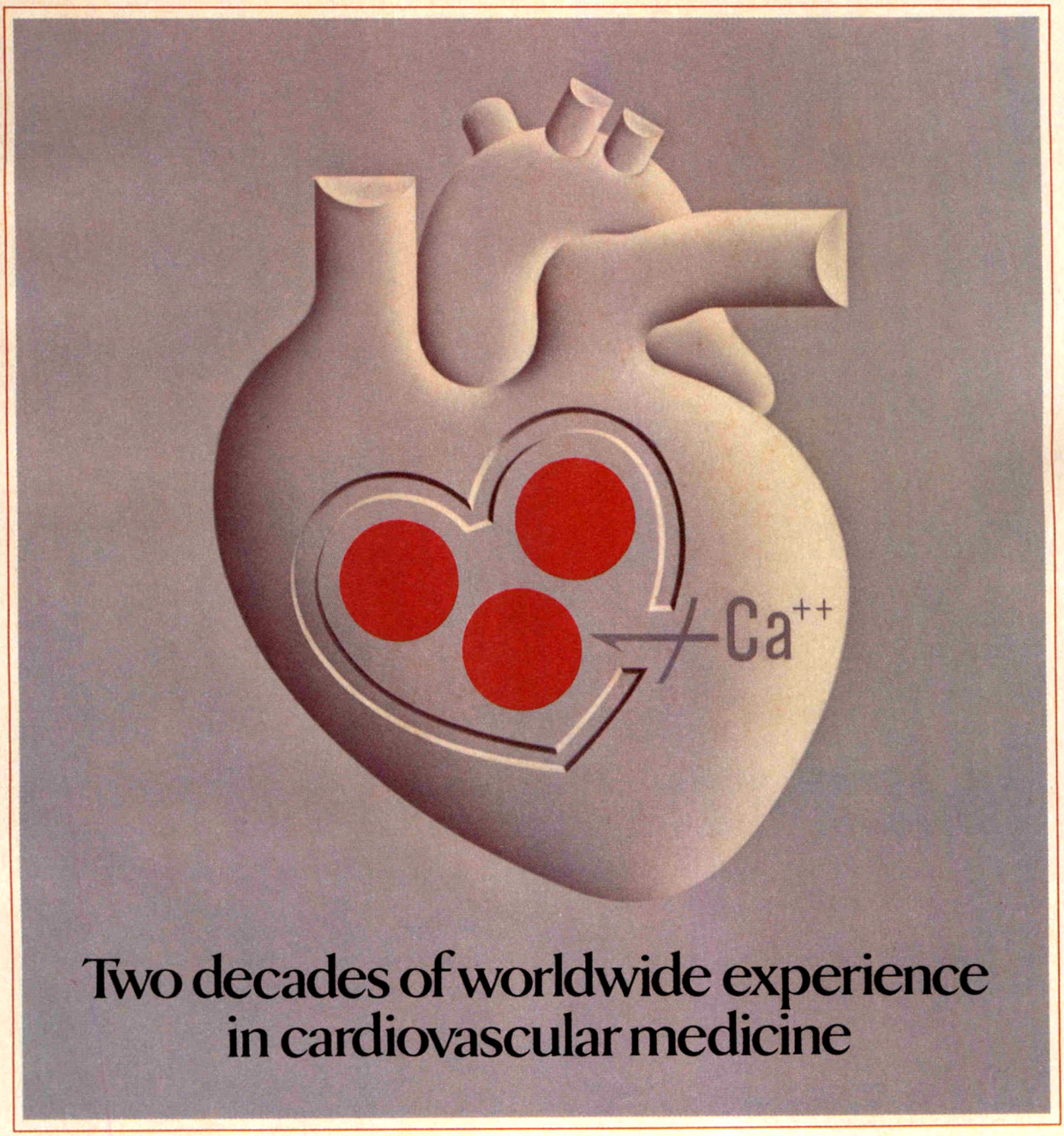
Limitations: Because this technique is semi-invasive, it is difficult to perform in infants or children without sedation. Also, unlike the transthoracic mechanical sector scanner, whose display angle can be continuously varied, the display angle of the transesophageal rotating scanner is only 180 or 260°. Modifications are now being developed to overcome these limitations.

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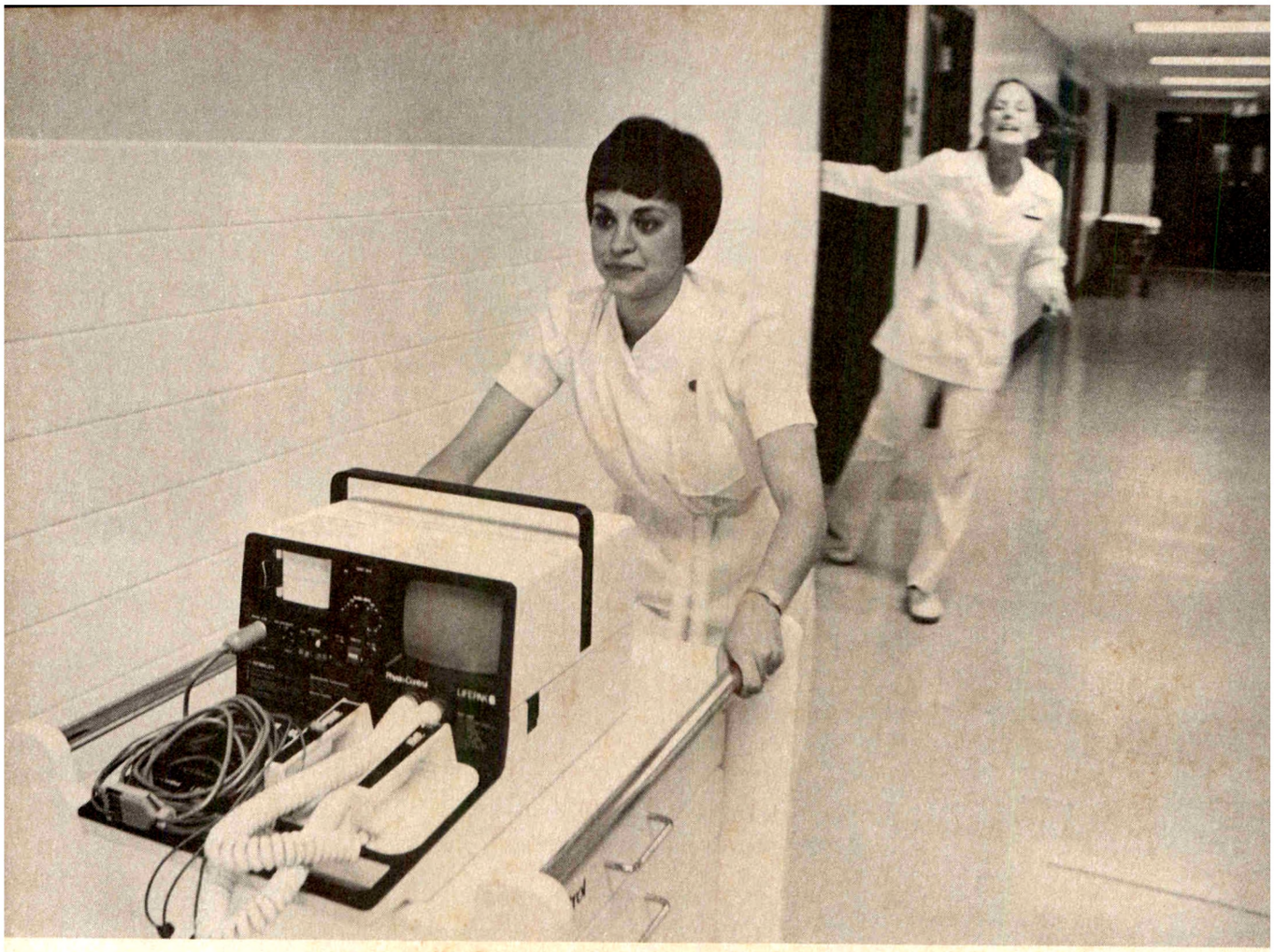
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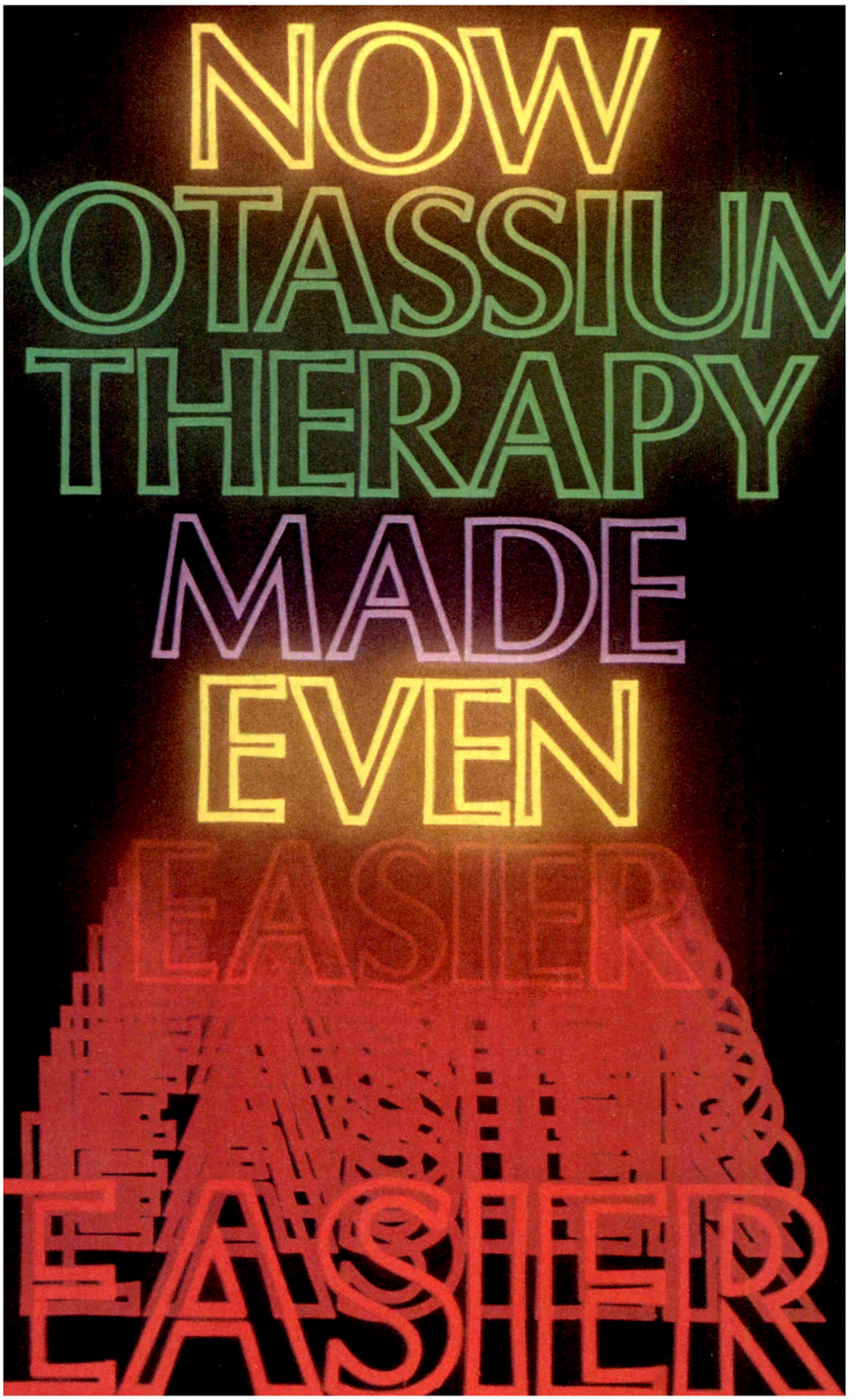
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All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) associated with wax-matrix tablets have been reported both in foreign countries and United States. In addition, perhaps because the wax-matrix preparations are not e coated and release potassium in the stomach, there have been reports of upper ga testinal bleeding associated with these products. The total number of gastrointe lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should b continued immediately and the possibility of bowel obstruction or perforation conside severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treate an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, pota acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonst hypokalemia in a patient with a clinical history suggesting some cause for potassium tion. In interpreting the serum potassium level, the physician should bear in mind that alkalosis per se can produce hypokalemia in the absence of a deficit in total body pota while acute acidosis per se can increase the serum potassium concentration into the n range even in the presence of a reduced total body potassium. The treatment of pota depletion, particularly in the presence of cardiac disease, renal disease, or acidosis re careful attention to acid-base balance and appropriate monitoring of serum electrolyte electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are sea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritati the gastrointestinal tract and are best managed by diluting the preparation further, takir dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warning Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excr mechanisms for potassium rarely causes serious hyperkalemia. However, if excr mechanisms are impaired or if potassium is administered too rapidly intravenously, p tially fatal hyperkalemia can result (see Contraindications and Warnings). It is importa recognize that hyperkalemia is usually asymptomatic and may be manifested only b increased serum potassium concentration and characteristic electrocardiographic cha (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of th interval). Late manifestations include muscle-paralysis and cardiovascular collapse cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sp diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

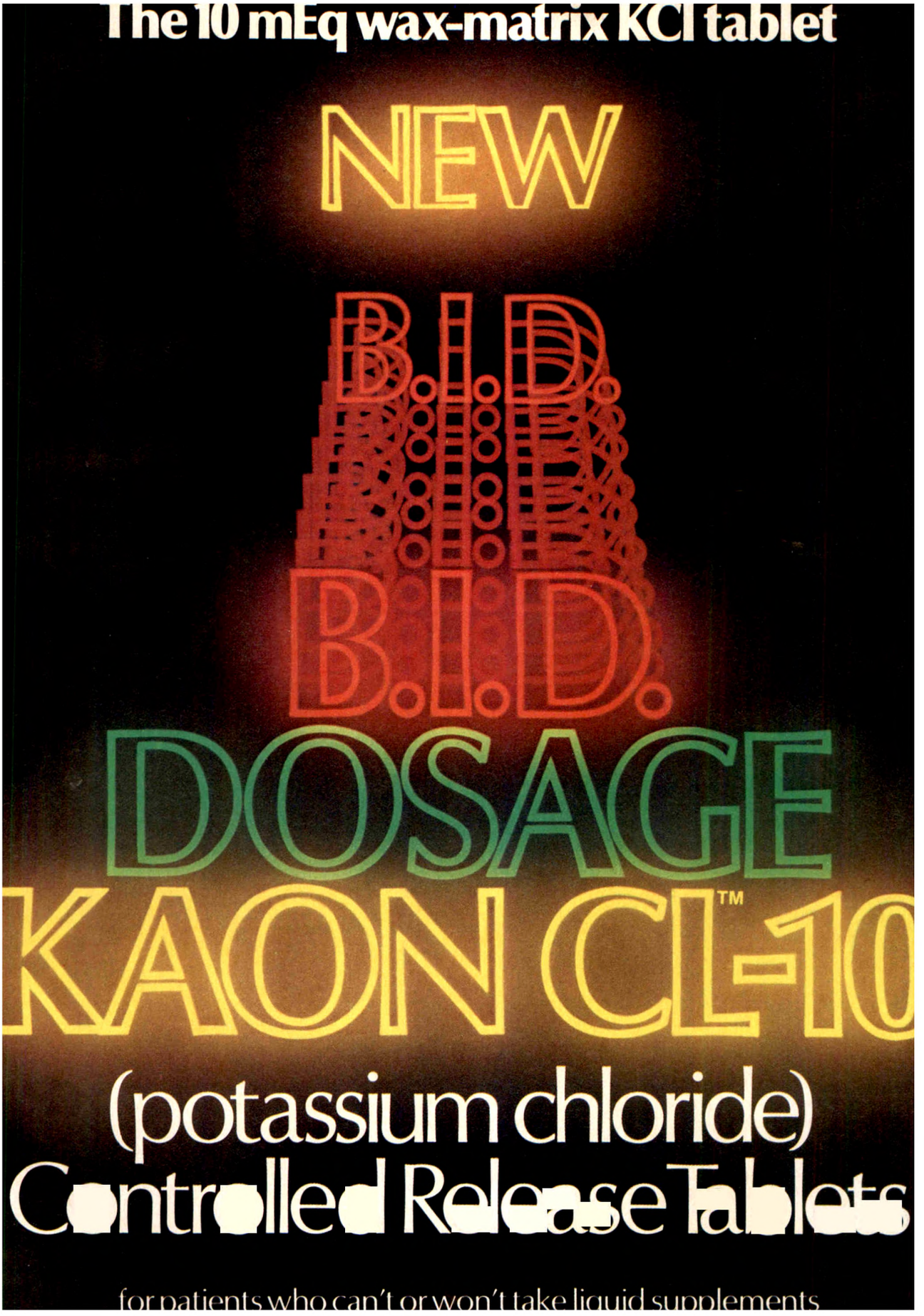
In treating hyperkalemia, it should be recalled that in patients who have been stabilize digitalis, too rapid a lowering of the serum potassium concentration can produce dig toxicity.

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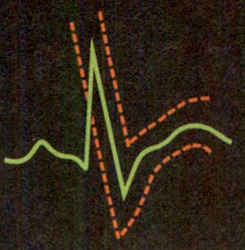
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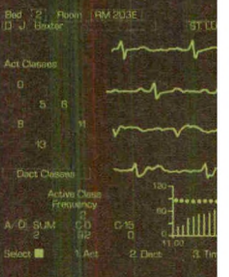
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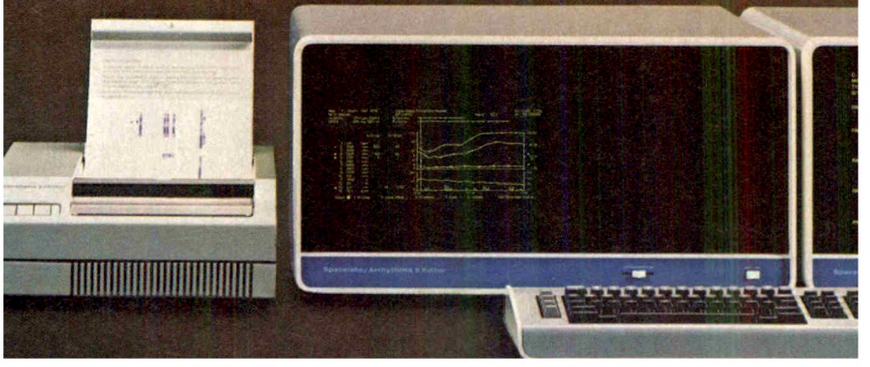
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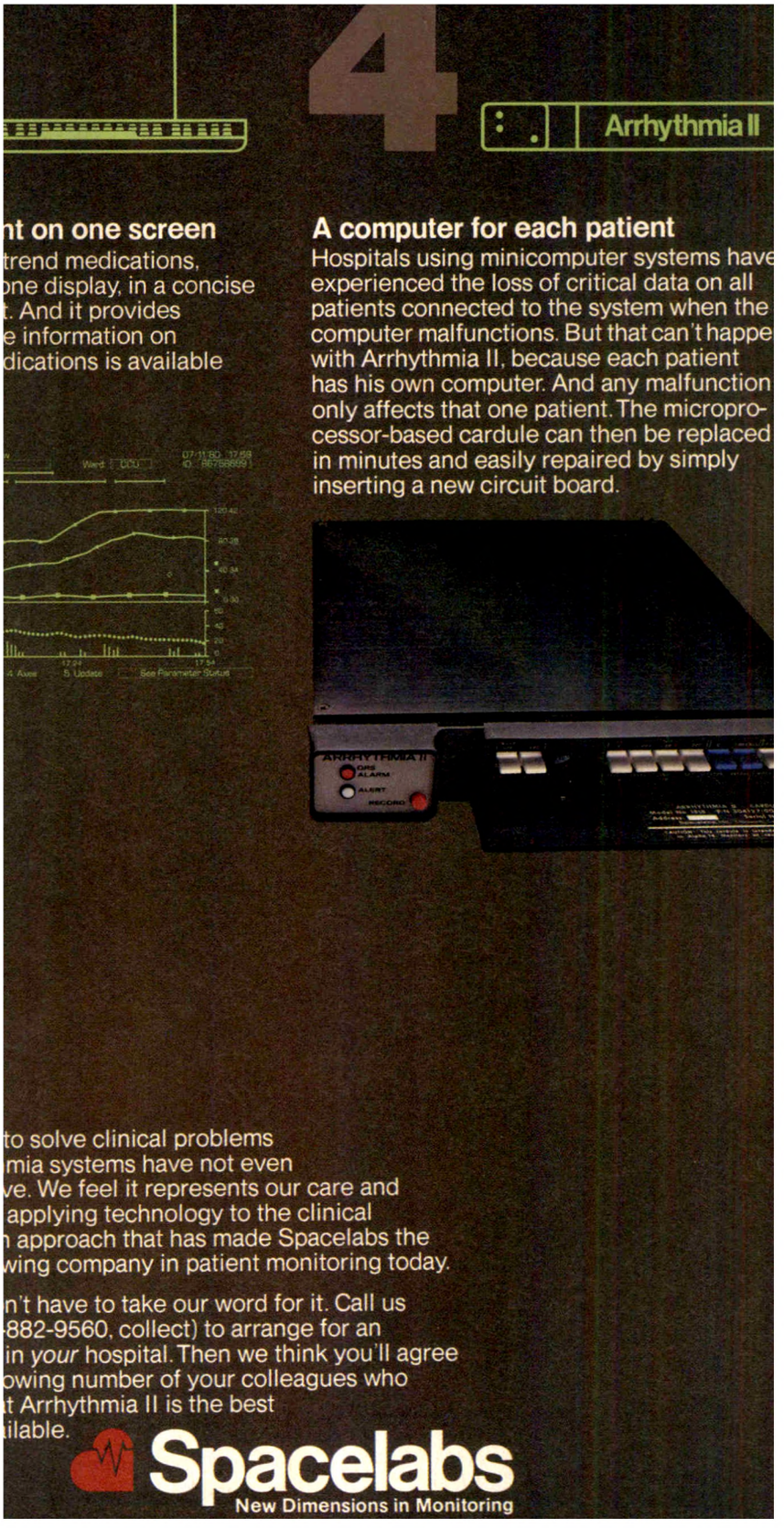
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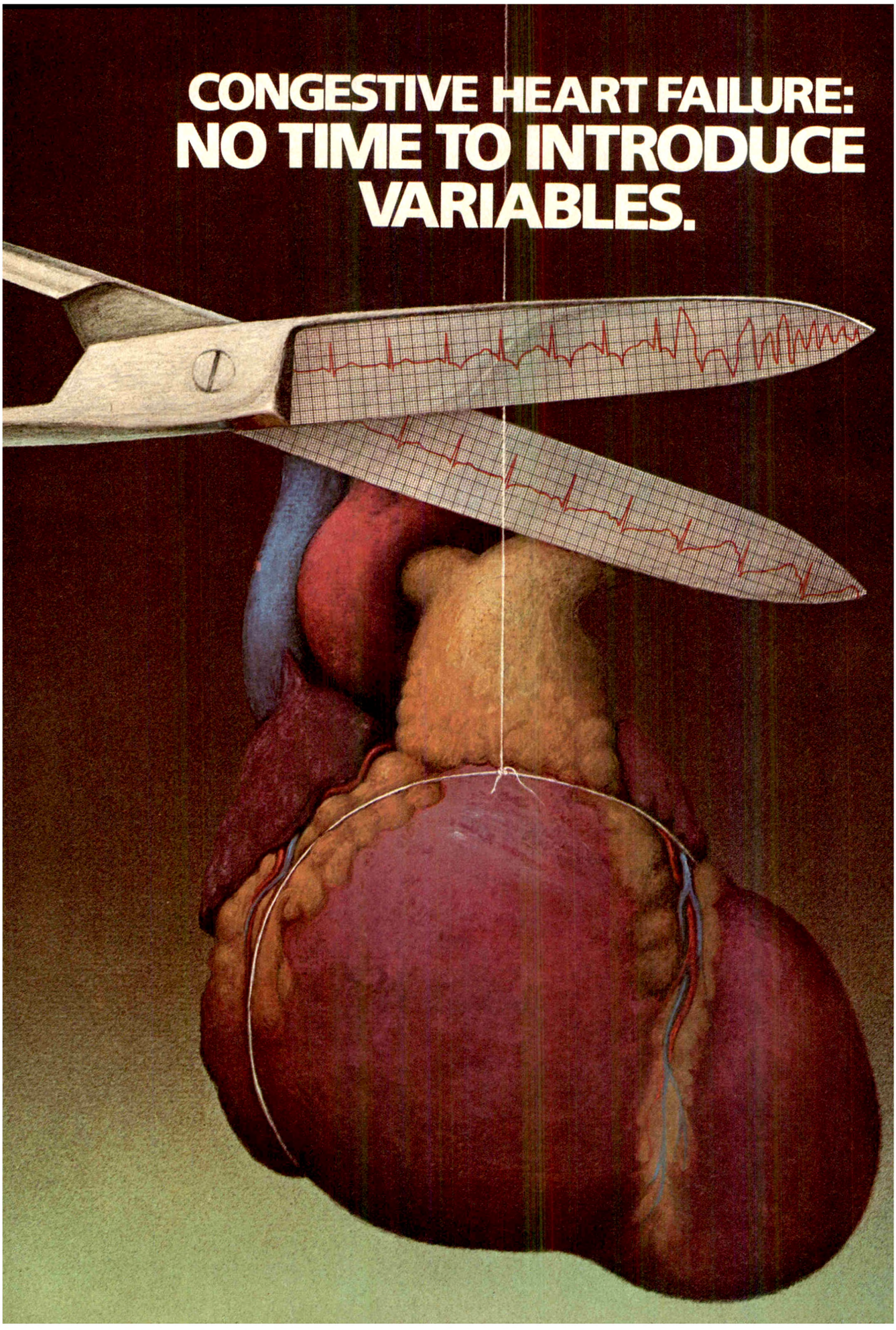
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LASIX® is the original brand of furosemide. It is LASIX® that established the standard for furosemide performance. It is LASIX® that is the subject of almost 6,000 published papers. It is LASIX® that has been used successfully in millions of digitalized patients over the past 14 years. And it is LASIX® that has a remarkable quality-control record—almost 8 billion tablets manufactured without a single product recall.

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Before prescribing, please consult complete product information, a summary of which appears on the following page.

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References: 1. Moe GK, Farah AE: Digitalis and allied cardiac glycosides, in Goodman LS and Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1970, pp 653-682. 2. Smith TW: Digitalis: Ions, inotropy and toxicity, editorial. *N. Engl. J. Med. 299*:545, 1978. 3. Rubinstein MH, Eastwood BA, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: The effect of lubricant type and concentration on the bioavailability of furosemide from 80 mg tablets: *J. Pharm. Pharmacol. 30* (suppl.):12P, Dec. 1978. 4. Rubinstein MH, Price EF, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: In vivo evaluation of the effect of five disintegrants on the bioavailability of furosemide from 40 mg tablets: *J. Pharm. Pharmacol. 29* (Suppl.):5P, Dec. 1977. 5. Rubinstein MH, Rughani JM, School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.: The effect of four tablet binders on the bioavailability of furosemide from 40 mg tablets: *Drug Development and Industrial Pharmacy* 4(6): 541-553 (1978). 6. HEW News, publication 79-6, U.S. Department of Health, Education and Welfare (Food and Drug Administration), March 30, 1979, pp 2-3.

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Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical
Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and
Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Ch
Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, Univers
Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—in *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reason this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actuall secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper book gives a comprehensive summary of all important fa of pre-excitation, plus the authors' personal experiences c follow-up studies of patients through many decades. It al brings a broad view of the literature and discusses the different structural and physiological aspects which form pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints at the same time evaluating relative strengths and weakne of each observation and hypothesis. There is brought a w here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiolo and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairm the Department of Medicine, The University of Alabama in Bir ham, and Physician-in-Chief, University of Alabama Hospitals.

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Prognostic Significance of Arrhythmia in Tetralogy of Fallot After Intracardiac Repair

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MILTON H. PAUL, MD, FACC
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Chicago, Illinois

The significance of arrhythmia and conduction defects was studied in 395 patients who underwent intracardiac repair of tetralogy of Fallot between 1958 and 1976. In 91 of these patients (group I), the median date of repair was 1964 and all underwent stress testing. In 107 patients (group II), the median date of repair was significantly later (1971), but all subjects were too young for stress testing. The remaining 197 patients (group III, median date of repair 1963) included all those who did not participate in stress testing or who had died; 42 of these patients were later excluded from analysis because of insufficient electrocardiographic records. The overall incidence of any form of arrhythmia (19 percent) was the same for each group. However, in group II (patients who underwent intracardiac repair more recently), no tachyarrhythmia was observed and there were fewer patients with 1° atrioventricular (A-V) block ($p < 0.001$) and more patients with complete right bundle branch block ($p < 0.001$) than in groups I and III. In two patients (both in group I), unexpected, late sudden death unrelated to strenuous physical activity occurred. Arrhythmia was least common in patients with primary intracardiac repair and more common in those with either palliation before intracardiac repair or multiple intracardiac repairs. In group I, 41 of 91 patients with arrhythmia of even minor degree at rest (n = 13) or exercise (n = 28) had a significantly larger heart, greater right ventricular pressure and lesser exercise performance than did those without arrhythmia, thus suggesting the presence of residual abnormality or dysfunction. No tachyarrhythmia was induced by exercise in this study. Patients with either arrhythmia or bifascicular block have generally had a benign course without strong evidence of progression of arrhythmia.

There has been a continuing interest in more precise quantitation of the results of intracardiac repair of tetralogy of Fallot and in the elucidation of factors that modify these results. Several studies[1–6] have explored the problem of arrhythmia in the late postoperative period. A series of reports have focused on the role of arrhythmias[1,3,4] and conduction defects[7–12] in late sudden, unexpected death.

This study is concerned with the incidence of arrhythmia at rest and during exercise in patients with tetralogy of Fallot after intracardiac repair and the prognostic significance of such arrhythmic events in general. It was prompted by our initial observations in 91 patients with tetralogy of Fallot, which suggested a more than casual relation between significant residual disease after intracardiac repair and the presence of arrhythmic events either on routine electrocardiography or during stress testing. Because these 91 patients were volunteers and therefore a selected group, we expanded this study to include all patients with tetralogy of Fallot who underwent intracardiac repair at the Children's Memorial Hospital, Chicago, between 1958 and 1976 and who had adequate records available. Specifically, we examined the relation of arrhythmic events to the type and number of palliative and corrective cardiac surgical procedures performed, changing operative and post-

From the Department of Pediatrics, Northwestern University Medical School, and The Willis J. Potts Children's Heart Center (Division of Cardiology), The Children's Memorial Hospital, Chicago, Illinois. This study was supported in part by Grants HL 17578 and GM 21293 from the National Institutes of Health, Bethesda, Maryland, Research Grant 74-1028 from the American Heart Association, Dallas, Texas, the Park Ridge Health Foundaton, Inc., Park Ridge, Illinois, and the Walden W. Shaw Foundation, Chicago, Illinois. Manuscript received April 1, 1980; revised manuscript received May 28, 1980, accepted May 29, 1980.

Address for reprints: Hans U. Wessel, MD, The Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Illinois 60614.

operative management, and postoperative and functional results as assessed by heart size, hemodynamic status and stress testing.

Methods

Study patients: The 395 patients who underwent intracardiac repair of tetralogy of Fallot between 1958 and 1976 were separated into three groups (Table I). Group I consisted of the 91 patients who volunteered for a long-term serial evaluation with stress testing. All had undergone one or more stress tests since 1968, and were at least 8 years old and 1 year postintracardiac repair when they entered the study. In this group there were two unexpected late sudden deaths, unrelated to stress testing or strenuous physical activity, occurring at ages 11 and 23 years, 3 and 13 years, respectively, after intracardiac repair.

Group II included 107 patients who underwent intracardiac repair but did not meet the preceding age criteria for entering the long-term follow-up study with stress testing when this study was initiated in 1968. This group differed from the other two groups in two other important aspects: The median date of intracardiac repair was significantly later (1971) than in groups I (1964) and III (1963) and all patients were managed relatively uniformly by a single surgical team.

Group III consisted of the remaining 197 patients who underwent intracardiac repair at the Children's Memorial Hospital until 1976. This group included those patients who died after repair and those who did not enter the long-term follow-up with stress testing when this study was initiated in 1968. Forty-two of these 197 patients were excluded from further analysis because electrocardiograms recorded after repair were not available. This modified group of 155 patients will be identified as group IIIA in the following discussion.

In addition to the two late sudden deaths in group I, there were 57 deaths in group III; thus, the overall mortality was 59 of 395 (14.9 percent). Forty-six of the 59 deaths occurred within 1 month of intracardiac repair and all but 3 within 1 year of repair. The mortality was the lowest in patients with primary intracardiac repair (21 of 192, 10.0 percent) or with palliation by subclavian-pulmonary shunt before repair (12 of 116, 10.3 percent). The mortality was significantly greater ($p < 0.001$) in patients with aortopulmonary (Potts) shunt (24 of 69, 34.8 percent) or pulmonary valvulotomy preceding intracardiac repair (2 of 6, 33.3 percent). None of the 12 patients with palliation by a Waterston-Cooley shunt died. The majority of these deaths occurred in the early surgical experience from 1958 to 1963.

The three groups had the same sex distribution (Table I). The median date of intracardiac repair was significantly later and the mean age significantly lower in group II than in groups I and III. The mean age at palliation was the same for groups I and II but was significantly greater in group III ($p < 0.001$). The length of follow-up study after intracardiac repair differed significantly among groups. However, if groups I and III are combined the average follow-up period does not differ significantly from that in group II.

Definition of arrhythmia: A patient was classified as having had arrhythmia if a routine 14 lead electrocardiogram obtained between the first preoperative visit and the last postoperative follow-up visit revealed even a single arrhythmic event. A patient in group I was classified as having had arrhythmia on exercise if even a single arrhythmic event was detected in the single lead (CM_5) recorded continuously during each exercise study; all exercise records included continuous electrocardiographic observation during a 3 minute period immediately before and during exercise and during at least 5 minutes of recovery from exercise.

Exercise studies: All initial exercise studies in group I were performed during a 2 day admission to the Clinical Research Center of the Children's Memorial Hospital, after informed consent had been obtained from the parents and subjects. All subjects exercised upright on an electrically braked cycle ergometer (Quinton Instrument Co., Model 840) which is recalibrated to 3 to 6 month intervals. We utilized a work protocol with stepwise loading[13,14] that began with a 3 minute period of rest with the patient sitting quietly on the cycle ergometer. Work was then begun at a rate of 100 kg-m/min and incremented by 100 kg-m/min at 1 minute intervals until the patient was unable to continue or maintain the pedaling cadence of 70 rpm. The test was evaluated in terms of heart rate at rest and at each work rate, duration of exercise in minutes, and working capacity (W_{170}) based on linear regression of heart rate on work rate between the 2nd and last minute of exercise. Results were expressed in absolute terms and as percent of predicted for age, height, weight and body surface area. Normal data were obtained in 221 male and 157 female normal volunteers who were recruited from a suburban school district.[13]

A bipolar electrocardiographic lead (CM_5) was monitored and recorded throughout each test. The heart rate was measured beat by beat with a highly accurate digital rate meter.[15] The heart rate at rest (sitting) was computed as the average rate during the 3 minute period before exercise. Exercise heart rates were averaged during the last 15 seconds at each work rate.

TABLE I
Patient Data

	Group I (n = 91)	p Value	Group II (n = 107)	p Value	Group III (n = 197)
Patients					
Male (n; %)	62; 68.1		68; 63.6		124; 62.9
Female (n; %)	29; 31.9		39; 36.5		73; 37.1
Year of intracardiac repair					
Median	1964;	<0.001	1971	<0.001	1963
Range	1959–1972		1961–1974		1958–1976
Age at operation (yr)					
Palliation	2.1 ± 1.3*	NS	1.9 ± 1.2†	<0.001	3.4 ± 2.5‡
Intracardiac repair	8.3 ± 4.6	<0.001	5.8 ± 3.6	<0.001	8.5 ± 4.9
Follow-up since repair (yr)	8.1 ± 3.8	<0.001	5.6 ± 2.0	<0.001	3.4 ± 3.8

* n = 52 of 91 (57.1%). † n = 54 of 107 (50.5%). ‡ n = 100 of 197 (50.8%).
For comparison of groups I and III versus group II: age at palliative procedure, $p < 0.05$; age at intracardiac repair, $p < 0.001$; follow-up since intracardiac repair, NS; n = number; NS = not significant; p = significance level of differences between group means.

TABLE II
Incidence of Arrhythmia and Conduction Defects on Routine Electrocardiography in 353 Patients With Tetralogy of Fallot

	Group I + IIIA		Group II		
	n	% of Group	n	% of Group	p Value
Total patients	246	100.0	107	100.0	
With arrhythmia	48	19.5	19	17.8	NS
PVC	19	7.7	6	5.6	NS
PAC, PNC	11	4.5	8	7.5	NS
Junctional escape or rhythm	12	4.9	8	7.5	NS
Supraventricular tachycardia	4	1.6	0	—	—
Atrial flutter	2	0.8	0	—	—
Ventricular tachycardia	5	2.0	0	—	—
Complete RBBB	152	61.8	86	80.4	<0.001
1° A-V block	60	24.4	2	1.9	<0.001
3° A-V block	9	3.7	2	1.9	NS
Bifascicular block	8	3.3	4	3.8	NS
Trifascicular block	10	4.1	0	—	<0.05

p = significance of chi-square statistic for comparison of incidence in combined group I + IIIa and group II. PAC = premature atrial complexes; PNC = premature nodal complexes; PVC = premature ventricular complexes; RBBB = right bundle branch block.

Results

Arrhythmic events on routine electrocardiography: The overall incidence rate of arrhythmic events on routine electrocardiography was 19 percent (67 of 353) and did not differ significantly among the three groups. Because there was no significant difference between groups I and IIIA other than availability for stress testing, these two groups were combined into a single group I + IIIA in subsequent analyses (Table II). The incidence of different types of premature beats and junctional escape beats or junctional rhythm also did not differ between group II and the combined group I + IIIA. However, no tachyarrhythmia was recorded in group II, but such arrhythmia observed in 11 (4.5 percent) of 246 patients in the combined group I + IIIA. There was a greater incidence of complete right bundle branch block ($p < 0.001$) but a lesser incidence of 1° atrioventricular (A-V) block ($p < 0.001$) and therefore of trifascicular block ($p < 0.05$) in patients in group II.

The relation between arrhythmia and the type and number of surgical procedures is summarized in Table III. Patients with primary intracardiac repair without reoperation for residual defects had the smallest incidence of arrhythmic events on routine electrocardiography. This relation was also apparent when the 59 nonsurvivors were analyzed separately.

The incidence of arrhythmia on routine electrocardiography was greater in patients who underwent a palliative procedure before intracardiac repair than in

TABLE III
Relation of Type and Number of Reparative Surgical Procedures to the Incidence of Arrhythmia on Routine Electrocardiography in 353 Patients With Tetralogy of Fallot

	Group I + IIIA				Group II				
	All	Arrhythmia n	Arrhythmia %	p^1	All	Arrhythmia n	Arrhythmia %	p^1	p^2
Cases (n)	246	48	19.5	NS	107	19	17.8	NS	NS
Type of operation									
Primary repair	121	14	11.6	—	53	6	11.3	—	NS
S-P shunt	69	17	24.6	<0.02	40	9	22.5	NS	NS
A-P shunt	48	13	27.1	<0.02	6	1	16.7	NS	NS
W-C shunt	3	2	66.7	<0.005	8	3	37.5	<0.05	NS
Brock	5	2	40.0	NS	—	—	—	—	—
Number of thoracic surgical procedures									
1	115	11	9.6	NS	53	6	11.3	NS	NS
2	105	21	20.0	NS	36	9	25.0	NS	NS
≥3	26	16	61.5	<0.001	18	4	22.2	NS	<0.001
≥2	28	18	64.3	<0.001	15	3	20.0	NS	<0.01
Palliative + 2 intracardiac repairs	20	14	70.0	<0.001	12	2	16.7	NS	<0.005
1 or 2 palliative procedures + intracardiac repairs	104	19	18.3	NS	42	11	26.2	NS	NS
Palliative procedure only	1	1	100.0	—	0	—	—	—	—

A-P = aortopulmonary (Potts) shunt; Brock = pulmonary valvulotomy; p^1 = significance of chi-square statistic; in each case the subgroup is compared with patients with primary intracardiac repair; p^2 = significance of chi-square statistic for comparison between group II and combined group I + IIIA; S-P = subclavian-pulmonary shunt; W-C = Waterston-Cooley shunt.

patients who had primary intracardiac repair. In combined group I + IIIA the increase was significant for all shunt procedures. These findings also suggested a relation between the incidence of arrhythmia and the number of surgical procedures in each patient. In combined group I + IIIA there was indeed a progressively increasing incidence of arrhythmia with an increasing number of surgical procedures. However, this increase in incidence was significant only for patients who had had three or more procedures ($p < 0.001$). However, further analysis of the data in Table III suggests that the increased incidence occurred primarily in patients with two or more intracardiac operations in contrast to multiple palliative procedures. The patients in group II also had a greater incidence of arrhythmia with shunt procedures proceding intracardiac repair and with multiple intracardiac repairs. However, the differences were not significant except for patients with a Waterston-Cooley shunt ($p < 0.05$). In contrast to findings in combined group I + IIIA there was no progressive increase in the incidence of arrhythmia in patients in group II who required two or more intracardiac repairs.

Arrhythmic events during exercise testing: The 91 patients in group I had had 400 stress tests since 1968. Arrhythmia during stress testing was revealed during one or more tests in 28 patients (30.8 percent). Tachyarrhythmia, ventricular standstill or ventricular fibrillation did not occur. Nineteen of these patients had single or multiple premature ventricular complexes, including two patients with runs of bigeminal rhythm. In two other patients premature ventricular complexes originated from two foci. Sixteen of the 28 patients had one or more premature atrial or junctional escape complexes; or both. Seventeen (60.7 percent) of the 28, including 12 with premature ventricular complexes, had only a single form of arrhythmia. The frequency with which arrhythmic events occurred during each of the three phrases of exercise varied. The arrhythmia was noted in 64.3 percent (18 of 28) during recovery, in 39.3 percent (11 of 23) during exercise and in 32.1 percent (9 of 28) during the resting phase before exercise. In the majority of patients premature complexes occurring at rest were suppressed when the sinus rate during exercise approached or exceeded the rate of the premature complexes and recurred with sinus slowing during recovery.

Exercise performance in patients with arrhythmia: A total of 41 patients (45.1 percent) in group I had arrhythmia (Table IV). The arrhythmia was noted only on routine electrocardiography in 13 patients and was observed during stress testing in 28 patients; in six of the latter, arrhythmia had also been noted on routine electrocardiography. Data from all 41 patients with arrhythmia on exercise testing and on routine electrocardiography were pooled because there were no significant differences in the variables listed in Table IV between the two subgroups. Moreover, the results of the analysis were not altered whether patients receiving digitalis at the time of evaluation were or were not included.

Patients with arrhythmia had a significantly reduced mean work performance when compared with patients without arrhythmia as assessed by duration of exercise, working capacity (W_{170}) and heart rate during the 4th minute of exercise. They also had a larger heart (as judged by cardiothoracic ratio) and smaller forced expired volume (vital capacity). Moreover, analysis of 54 patients in group I who underwent cardiac catheterization after intracardiac repair showed significantly higher average peak systolic and end-diastolic right ventricular pressures in those with arrhythmia.

Discussion

Role of conduction defects in postoperative sudden death: Studies of conduction defects and arrhythmia after intracardiac repair of tetralogy of Fallot initially were focused on the risk of sudden death associated with these complications due to complete heart block and ventricular ectopic rhythm.[1,12] A large inci-

TABLE IV
Hemodynamics and Exercise Performance After Intracardiac Repair of Tetralogy of Fallot in 91 Patients With or Without Arrhythmia at Rest or Exercise, or Both

	Patients With Arrhythmia at Rest or on Exercise (n = 41)	Patients With No Arrhythmia (n = 50)	p Value
Age at repair (yr)	8.87 ± 3.93	7.19 ± 3.2	<0.05
Follow-up since repair (yr)	8.3 ± 3.4	8.3 ± 3.8	NS
CT ratio at last follow-up	0.541 ± 0.07	0.504 ± 0.049	<0.01
P_{RV} (mm Hg)	71.2 ± 28.5 (n = 23)	55.3 ± 21.4 (n = 31)	<0.05
P_{RV} (ed) (mm Hg)	9.6 ± 3.3 (n = 23)	7.5 ± 1.8 (n = 31)	<0.01
FEV (% of predicted*)	79.9 ± 16.8	87.3 ± 14.4	<0.02
Heart rate at rest (beats/min)	84.0 ± 15.6	85.6 ± 12.7	NS
4th minute exercise heart rate (% of predicted†)	113 ± 19.2	101 ± 15.2	<0.01
Duration of exercise (% of predicted†)	66.1 ± 18.2	87.9 ± 20.3	<0.001
W_{170} (% of predicted†)	77.4 ± 24.8	99.6 ± 29.4	<0.001

* Predicted for height. † Predicted for age.
CT = cardiothoracic; FEV = forced expired volume; P_{RV} = peak systolic right ventricular pressure; P_{RV} (ed) = end-diastolic right ventricular pressure; W_{170} = working capacity.

dence of sudden death was reported in patients with complete right bundle branch block and left anterior hemiblock (bifascicular block) after surgical treatment of tetralogy of Fallot.[7] Many of these patients had had transient complete heart block in the intraoperative or early postoperative period. However other studies reported a benign course in patients with bifascicular block.[3,9–12] On the basis of clinical, anatomic and experimental evidence, Steeg et al.[10] concluded that such a different outcome in patients with the same scalar electrocardiographic findings could be reconciled by assuming different mechanisms for the observed conduction defects. They postulated that in patients with a benign long-term course the conduction defect is likely due to a peripheral disruption of the conduction system by the ventriculotomy.[16,17] Conversely, transient or permanent complete heart block and increased late mortality is the consequence of more proximal injury to the specialized A-V conduction system.

Role of arrhythmia in postoperative sudden death: Similarly, it has been shown that arrhythmia, notably ventricular ectopic rhythm, presages an increased risk of sudden death in patients after repair of tetralogy of Fallot.[1,3,4] James et al.[1] reported unexpected cardiac arrest in 4 of 220 patients without a history of bifascicular block or transient complete heart block. In each patient who died suddenly, postoperative electrocardiograms had demonstrated ventricular ectopic rhythm and in one patient multifocal premature ventricular complexes were noted during a stress test and short bursts of ventricular tachycardia during the recovery period. Gillette et al.,[4] in a review of 51 patients with surgically treated tetralogy of Fallot, found 9 with ventricular ectopic rhythm, 3 of whom died suddenly. These and other studies[1,4,5] also suggest that patients with ventricular arrhythmia often have poor surgical results with evidence of significant residual disease and abnormal hemodynamic status. Our study supports this view and provides evidence that even minor rhythm disturbances—that is, single arrhythmic events that would be considered of little importance in the absence of heart disease—take on added significance in patients after surgical treatment of tetralogy of Fallot. The patients with rhythm disturbances had a larger heart size, higher peak systolic and end-diastolic right ventricular pressures and a poorer exercise performance than patients without arrhythmia (Table IV). We therefore view such rhythm disturbances as a nonspecific manifestation of significant residual disease or myocardial dysfunction until proved otherwise by appropriate studies. The relation between arrhythmia and residual disease is further supported by the greater incidence of arrhythmia in patients with multiple reparative surgical procedures than in patients with primary intracardiac repair alone (Table III).

Incidence of postoperative arrhythmia and conduction defects: Because conduction defects and rhythm disturbances are to a major extent surgical complications of intracardiac repair, it is not surprising that their incidence and the attendant morbidity and mortality should vary among reported series. In contrast to Issenberg et al.,[6] we did not observe a large incidence of severe ventricular arrhythmia (Lown stages 3 to 5) with exercise when ventricular ectopic rhythm was present at rest. In the majority of our patients ectopic rhythm was suppressed when the sinus rate approached or exceeded the rate of the ectopic pacemaker during exercise. We found no tachyarrhythmia induced by exercise and observed ventricular couplets in only two patients. We also found no relation between bifascicular and trifascicular block or arrhythmia and late sudden death. Neither of the two patients in group I who died suddenly had bifascicular block. In one of these patients no arrhythmia was detected on routine electrocardiography and none was observed during a single exercise study. However, in the second patient, 2 years after a second exercise study failed to provoke ectopic rhythm of any kind, a routine electrocardiogram demonstrated a single couplet of premature ventricular complexes. Six months later the patient died suddenly at home at age 23 years.

Role of age and length of follow-up: Other investigators[1,5] have commented on the presence of ventricular ectopic rhythm in older patients with postoperative tetralogy of Fallot and have suggested that this may be a progressive problem, developing as postoperative intervals become longer and patients enter their 20s.[5] However, many of the patients in their 20s reported on to date were among those patients who underwent operation during the early experiences with intracardiac repair (1955 to 1965). Moreover, many of these patients underwent palliative and corrective procedures at an older age than is usual today and they are not representative of the majority of such patients now being followed up. In our study, most patients were followed up close to a decade after intracardiac repair, and did not manifest a tendency toward increasing frequency or severity of ventricular ectopic rhythm. This finding is in accord with the generally stable hemodynamic status of the majority of these patients.[14]

Role of advanced surgical techniques and multiple operations: If conduction defects and arrhythmia are primarily related to surgical aspects of intracardiac repair, it is reasonable to assume that their incidence would decrease in patients who had had more recent repair (group II) and had thus benefited from continuing advances in surgical and perfusion techniques not available to those undergoing earlier repair (group I and IIIA). To some extent our data support this hypothesis. Although there was no decrease in the overall incidence of arrhythmia in patients in group II, there were important qualitative differences (Table II). Patients in group II had no tachyarrhythmia and had a much smaller incidence of first degree A-V block ($p < 0.001$) and trifascicular block ($p < 0.05$), but a larger incidence of complete right bundle branch block ($p < 0.001$). These findings suggest that there was less damage to the central portion of the specialized A-V conduction system as a result of refinement of the techniques for closure of the ventricular septal defect and repair of the right ventricular outflow tract. As in combined group I and IIIA, patients in group II with

more than one reparative surgical procedure (Table III) had roughly twice the incidence of arrhythmia compared with those with only primary intracardiac repair. However, patients in Group II unlike those in group I and IIIA who had undergone multiple intracardiac procedures did not have any further increase in the incidence of arrhythmia.

Clinical implications: Because the patients in this study with bifascicular block or arrhythmia, or both, have had a benign course without strong evidence of progression of arrhythmia, we have been reluctant to administer prophylactic antiarrhythmic therapy routinely. However, the patients are followed up with periodic routine electrocardiography and exercise testing to detect any progression in arrhythmic activity or deterioration in cardiovascular performance. Twenty-four hour electrocardiographic monitoring is recommended when arrhythmic activity appears, increases with increasing work rates or is particularly prevalent during early recovery from exercise when the rate of cardiac slowing is maximal; the latter finding suggests that the patient may be prone to arrhythmia during sleep. It remains to be shown if patients with tetralogy of Fallot whose heart is repaired in early childhood (less than age 2 years) or infancy with the use of more recent and advanced surgical techniques will have the same incidence of arrhythmia as those operated on in later childhood and adolescence.

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Pulsed Doppler Echocardiographic Evaluation of the Cyanotic Newborn: Identification of the Pulmonary Artery in Transposition of the Great Arteries

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During M mode echocardiographic evaluation of cyanotic newborn infants, one may find two ventricles and two great vessels, but not have proof of their identity. Identification of the great vessels is important in evaluation of possible transposition of the great arteries. In a series of 68 cyanotic neonates pulsed Doppler echocardiography was applied to test the hypotheses that (1) a patent ductus arteriosus in present in most cyanotic neonates, (2) the great vessel that receives diastolic ductal flow is the pulmonary artery, and (3) specific noninvasive identification of pulmonary artery will allow diagnosis or exclusion of transposition of the great arteries. On M mode examination, the relations of the great vessels were normal in 43 infants; in all, pulsed Doppler echocardiography detected a patent ductus arteriosus flowing into a normally positioned pulmonary artery. The cyanosis in these 43 patients was later proved to be of pulmonary origin. In eight infants, the relation of the great vessels suggested transposition, and in all eight, Doppler echocardiography detected a patent ductus flowing into the posterior great vessel, proved at angiocardiography to be the transposed pulmonary artery. In 17 patients, the relation of the great vessels was front to back, neither "normal" nor suggestive of classic d transposition. A patent ductus arteriosus, detected with pulsed Doppler echocardiography in all 17, flowed into the anterior great vessel in the 14 normal infants, and flowed into the transposed pulmonary artery in the 3 with proved transposition. It is concluded that ductal patency is prevalent in cyanotic neonates, and that pulsed Doppler echocardiographic detection of ductal flow can define the pulmonary artery; such definition is most helpful in resolving the question of transposition in infants with a relation of the great vessels that is neither normal nor suggestive of transposition.

In cyanotic neonates with possible heart disease, M mode echocardiography is useful in demonstrating the presence, location and relation of cardiac structures. If all structures are identified, in the expected location and with normal relations, the presence of cyanotic congenital heart disease is unlikely. If the expected structures are not identified on M mode echocardiography, appear significantly abnormal or have unusual relation, invasive study is usually required to establish the diagnosis. However, there is a group of cyanotic patients whose M mode studies reveal the presence of two ventricles, two atrioventricular valves, as well as two semilunar valves that have an other than "normal" relation. In such infants, the question of transposition of the great arteries is of special importance. That is, if transposition is present, cardiac catheterization, angiocardiography and Rashkind atrial septostomy are urgently needed. If transposition is not present, and the remainder of the M mode study is normal, invasive study is usually not needed, and certainly not on an emergent basis. Needless cardiac catheterization could then be avoided if one knew which great vessel was the aorta and which

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the pulmonary artery, since such knowledge could confirm or exclude the presence of transposition.

We have applied pulsed Doppler echocardiography in a prospective series of 87 cyanotic neonates in whom an ultrasonic examination was requested to help in the evaluation of significant cyanosis. The hypotheses to be tested in this series were: (1) patent ductus arteriosus will be present in the majority of cyanotic newborn infants, (2) the vessel that receives diastolic ductal flow is the pulmonary artery, and (3) noninvasive identification of the pulmonary artery will resolve the question of transposition of the great arteries.

Pulsed Doppler echocardiography is a relatively new noninvasive technique that complements traditional M mode echocardiography.[1] As in the familiar M mode technique, ultrasonic pulses are emitted through a hand-held transducer. And, as the pulses encounter cardiac structures, a portion of the ultrasound is reflected or back-scattered, received by the transducer and then processed to record the position of structures with respect to depth and time. In pulsed Doppler echocardiography, a portion of the ultrasonic pulses is reflected from the cardiac structures and a smaller portion is back-scattered from the moving blood cells within the cardiac chambers or vessels. If the blood cells are moving, the frequency of the sound back-scattered from those moving objects will be shifted in proportion to the velocity of the object, and a Doppler shift will be detected. The returning signal is of higher frequency than the emitted signal if the motion is toward the transducer and of lower frequency if the motion is away from the transducer. Using a range-gated pulsed Doppler device one may evaluate such Doppler shifts at known depths[2] as well as the uniformity of the Doppler shift over a small teardrop-shaped area that has been termed the sample volume. If all blood cells are moving uniformly at the position of the sample volume, a smooth audio and spectral record are produced by the Doppler unit. If disturbed or turbulent flow is present at the position of the sample volume, a rough audio sound is produced along with a flow record of disturbed flow (Fig. 1).

Methods

Study patients: The series is comprised of 87 neonates who had their initial cardiac evaluation for cyanosis at ages ranging from 1 to 21 days. Seventy of the patients were seen at ages less than 7 days. Ultrasonic evaluation was requested because of clinically apparent cyanosis, after the arterial partial pressure of oxygen failed to rise above 100 mm Hg with an inspired oxygen concentration of 90 to 100 percent. Most patients were suspected of pulmonary disease such as hyaline membrane disease, pneumonia or aspiration. Some patients were receiving assisted ventilation at the time of examination. The Doppler examinations were performed as part of a cardiologic consultation, so that on many occasions the examiner was familiar with the differential diagnosis. During the time period covered in the series, there were six infants whose Doppler examinations could not be accomplished from a standard precordial approach; they were examined from a nonstandard subxiphoid approach and were excluded from the series. In 13 infants, M mode echocardiography strongly suggested the presence of cyanotic heart disease (single great vessel in 7, aortic overriding with small pulmonary valve in 6); these patients were also excluded from the series because Doppler determination of great vessel identity would not alter the diagnosis of cyanotic heart disease. With these exclusions, 68 patients remained for analysis.

Pulsed Doppler echocardiography: The examinations were performed with Advanced Technology Laboratories Pulsed Echo units 600A, or 600B, and pulsed Doppler units 400A (5 megahertz) or 500A (3 megahertz). The ultrasonic examinations began with the M mode echocardiographic examination using a 5 megahertz transducer. The standard precordial left parasternal approach was used for visualization of cardiac structures and great vessel relation. The great vessel relation, on the basis of multiple sweeps, were labeled as *normal* (left-sided vessel anterior, right-sided vessel posterior), *front to back* (both vessels visualized with one directly anterior to the other), or *probably transposed* (anterior vessel to the right and posterior vessel to the left).

Pulsed Doppler examinations followed the M mode examinations for evaluation of the characteristics of intracardiac and great vessel blood flow. As previously described,[1,2] the sample volume is guided throughout the heart and great vessels in search of normal or abnormal blood flow characteristics. The examination is considerably aided by the audio output for guiding the sample volume through the various

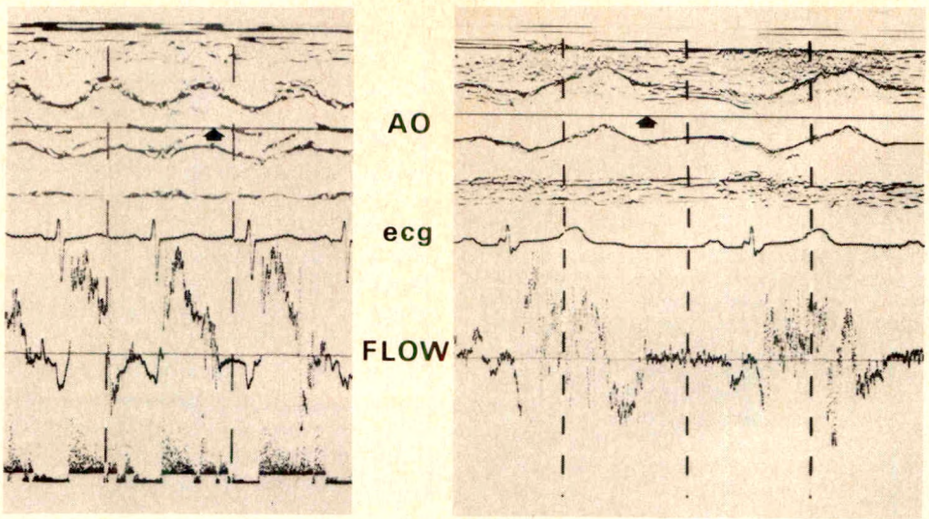


FIGURE 1. Pulsed Doppler echocardiographic flow records of smooth flow and rough flow. Both panels are from a standard precordial approach, with visualization of the aortic (AO) root. The sample volume is in the aortic root. **Left panel,** the flow record from the position of the sample volume is composed of rather closely grouped dots, indicating smooth flow. Such a flow record would be accompanied by a smooth audio sound. Systolic flow is above the FLOW line, indicating flow toward the transducer. **Right panel,** the systolic portion of the flow record is composed of very scattered dots, indicating rough systolic flow at the position of the sample volume. Such a flow record would be accompanied by a rough audio output. ecg = electrocardiogram; FLOW = time-interval histographic flow record.

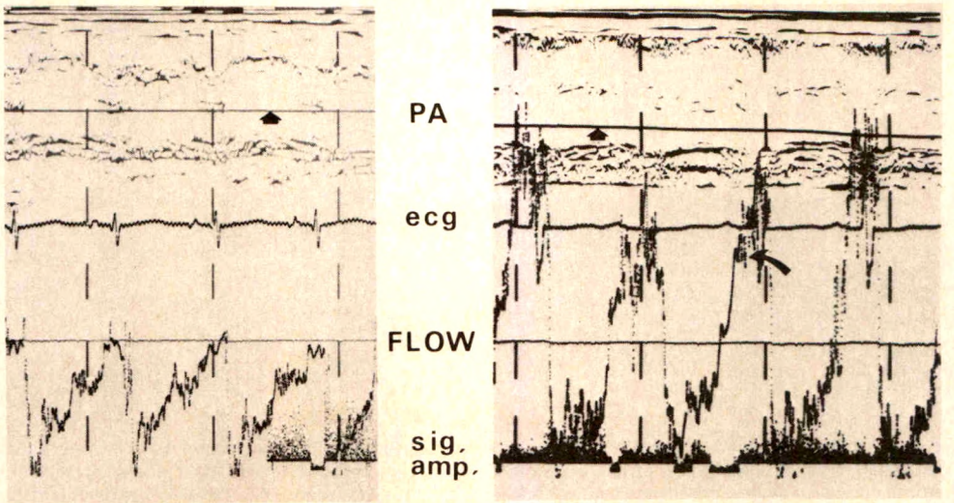


FIGURE 2. Pulsed Doppler echocardiographic flow records of normal pulmonary arterial flow and pulmonary arterial flow with patent ductus arteriosus. Both panels were obtained from the precordial approach with placement of the sample volume (**short arrows**) in the pulmonary artery (PA), distal to the pulmonary valve. **Left panel,** systolic flow is below the FLOW line, away from the precordial transducer, representing flow from the right ventricle into the pulmonary artery. The signal amplitude (sig. amp.) indicator channel, at the far bottom of the figure, has been blanked for a portion of the record. **Right panel,** systolic flow, similar to that on the left, is below the FLOW line. However, in diastole there is marked deflection of the flow record above the FLOW line, indicating diastolic flow toward the precordial transducer (**curved arrow**). The dots composing this portion of the record are somewhat scattered. The diastolic jet flowing into the pulmonary artery, (**curved arrow**) indicates a patent ductus arteriosus. Unidentified abbreviations as in Figure 1.

chambers and vessels. Abnormal blood flow characteristics may be detected by harsh audio output, or by dot scatter on the time interval histogram (Fig. 1). Special attention was given to great vessel blood flow characteristics for detection of a patent ductus arteriosus. Specifically, the sample volume was moved from the respective outflow tract to the great vessel, in search of disturbed blood flow. A patent ductus was deduced when the strip chart recorded turbulent diastolic flow directed toward the precordially placed transducer (Fig. 2). Detection of continuous turbulent flow in the pulmonary artery was felt consistent with a patent ductus, but not diagnostic.[3] Turbulence was considered to be present when a rough audio sound and dot scatter on the time interval histogram were present. For recording the time interval histographic flow record, the Doppler unit was set according to manufacturer's instructions with the signal amplitude indicator. The baseline of the signal amplitude indicator "jumps" at times of flow with broadening of the channel during periods of flow (Fig. 1 and 2). Such broadening is indicative of the strength of the backscattered Doppler signal, and it is desirable to have a moderate degree of broadening, but not such severe broadening that the entire channel "squares-off" at the top.

On the basis of the Doppler examinations, the pulmonary artery was defined as that great vessel receiving diastolic ductal flow (Fig. 3 and 4). Verification of great vessel relation was made by cardiac catheterization and biplane cineangiocardiography in 22 cases, and postmortem examination in 13. Transposition of the great arteries was defined as origin of the aorta from the right ventricle and origin of the pulmonary artery from the left ventricle.[4] Forty-three patients did not have invasive study. They eventually became acyanotic during nursery stay, and were discharged without evidence of intrinsic cardiac defects.

Results

The patients were grouped on the basis of M mode determination of the relation of great vessels, pulsed Doppler diagnosis and the final diagnosis (Table I). There were patients with cyanotic congenital heart disease in each great vessel category. Of the entire 68 patients, there were 2 (ages 1 and 3 days) in whom a ductal jet could not be found by the Doppler technique. In these two, both great vessel flows were normal. Pulsed Doppler echocardiography diagnosed patent ductus arteriosus in 66 of the 68 patients (discrete jet recorded), supporting the hypothesis that ductal patency is the rule in newborn infants with cyanosis.

Group with normal great vessel relation: Forty-three patients had a normal great vessel relation on M mode study; that is, the anterior great vessel was to the left of the posterior great vessel. Of these, two had no

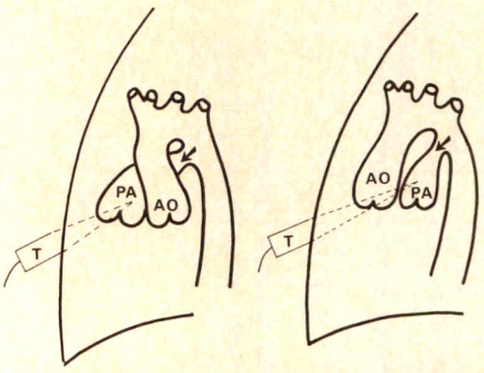


FIGURE 3. Schematic diagram of approach to pulmonary artery and patent ductus arteriosus in the normal subject and in the subject with transposition of the great arteries. **Left,** in the absence of transposition, flow from the patent ductus arteriosus is obtained in the anterior vessel, a normally positioned pulmonary artery (PA). On the right, with transposition of the great arteries, the ductal flow is into the posterior vessel, a transposed pulmonary artery. The **arrow** indicates flow from the aorta to the pulmonary artery. AO = aorta; T = transducer on the precordium.

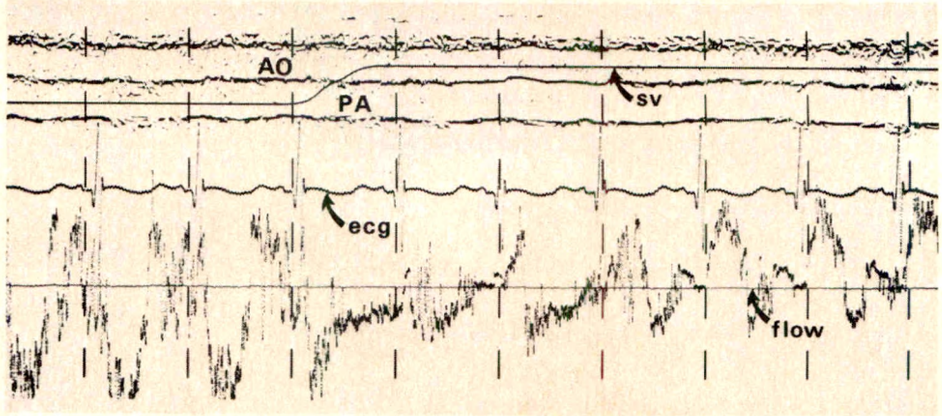


FIGURE 4. Pulsed Doppler echocardiographic flow record of aorta and pulmonary artery in transposition of the great arteries. **Top,** the compressed M mode tracing indicates the presence of two great vessels, with the sample volume in the posterior vessel at left and in the anterior vessel at right. **Left,** the flow pattern of the posterior vessel reflects diastolic inflow from a patent ductus arteriosus (see Fig. 2, right) and therefore the posterior vessel is the pulmonary artery (PA) as it receives ductal flow. **Right,** a normal systolic and diastolic flow pattern is obtained with the sample volume (sv) in the other great vessel, the transposed aorta (AO). There is some nonflow scattering of dots in the center of the figure, as the sample volume traverses the position of the aortic valve leaflets. Unidentified abbreviations as in Figure 1.

Doppler evidence of a left to right ductal shunt and were presumed to have undergone spontaneous ductal closure. A patent ductus was detected in the remaining 41 patients. In 16 with uncomplicated patent ductus arteriosus, cyanosis was attributed to coexisting hyaline membrane disease. In 14, abbreviated diastolic ductal flow was noted, consistent with severe pulmonary hypertension but still with some left to right ductal shunt.[5] In three infants, the ductus was associated with ventricular septal defect; the specific diagnosis of that defect was not possible with the M mode technique but was made with pulsed Doppler echocardiography. In four patients, the ductus was associated with tricuspid insufficiency. One patient had coarctation of the aorta and retrospectively was considered to have also had aspiration pneumonitis. Three patients with important heart disease (congenitally corrected transposition of the great arteries, ventricular septal defect, pulmonary

TABLE I

Summary of 58 Cases

Pulsed Doppler Diagnosis	n	Final Diagnosis
Normal (anterior great vessel to left of posterior vessel)		
PDA	30	PDA, HMD, lung dis.
PDA, TR	4	PDA, R-L atrial shunt
VSD, PDA	3	Same
Normal	2	HMD
Pulmonary atresia, PDA	1	Same
Critical PS, PDA	1	Same
PDA, coarctation	1	Same, lung dis.
I-TGA, PDA, ?VSD	1	I-TGA, VSD, PS, PDA
Total	43	
Front to Back		
PDA	9	PDA, HMD, lung dis.
TGA, PDA	2	Same
PDA, TR	1	Same
TGA, PDA, ?VSD	1	Same, common ventricle
PS, PDA	1	Same
VSD, PDA	1	Same, HMD
TAPVR, PDA	1	Same
Tricuspid atresia, PDA	1	Same
Total	17	
Probably Transposed (anterior great vessel to right of posterior vessel)		
TGA, PDA	6	Same
TGA, PDA, ?PS, ?VSD	2	Same, with PS and VSD
Total	8	

ASD = atrial septal defect; HMD = hyaline membrane disease; I-TGA = congenitally corrected transposition of the great arteries; ventricular inversion; lung dis = other pulmonary parenchymal disease; PDA = patent ductus arteriosus; PS = pulmonary stenosis; R-L = right to left; Same = final diagnosis same as predicted with pulsed Doppler echocardiography; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; TR = tricuspid regurgitation; VSD = ventricular septal defect.

valve stenosis, pulmonary valve atresia, and critical pulmonary stenosis) would have been recognized as having heart disease from the M mode study without the Doppler examination, but the latter clarified the question of transposition and therefore the question of heart disease of the cyanotic variety.

Group with front to back great vessel relation: In 17 infants in whom two great vessels were identified with a front to back relation, neither vessel seemed clearly to be to the right or left of, or superior or inferior to, the other vessel on M mode echocardiography. In 7 of the 17, important cardiac defects were present. Of prime concern was the possibility of transposition of the great vessels. On the basis of defining the pulmonary as that vessel receiving the ductus, Doppler echocardiography correctly predicted the presence of transposition in the 3 infants who had it, and documented the absence of transposition in the remaining 14. Pulsed Doppler echocardiography detected the specific diagnostic flow abnormalities in the patients with ventricular septal defect, pulmonary stenosis, and total anomalous pulmonary venous return.[6–8] The M mode study led to visualization of only one atrioventricular (A-V) valve in the patient with tricuspid atresia, but Doppler study resolved the question of transposition.

Transposition of great vessels group: Eight patients had an M mode great vessel relation of the sort usually indicative of "d-transposition" (the anterior great vessel to the right of the posterior vessel), and that relation was confirmed at catheterization. Two had, in addition, a ventricular septal defect and pulmonary stenosis. In all eight, a patent ductus was present with blood flowing into the posterior great vessel during diastole, thereby identifying this vessel as the pulmonary artery.

Discussion

The M mode echocardiographic recognition of transposition of the great arteries, as described by Gramiak et al.,[9] allows successful detection of d-transposition in many patients. In our series, 8 (73 percent) of 11 patients with proved transposition had a classic d-transposition relation demonstrated on M mode echocardiography. However, in a larger series of patients, the typical d-transposition great vessel relation may be present in as few as 50 to 69 percent of patients with proved transposition.[10–12]

Some investigators[13] have described use of systolic time intervals to aid in identification of the pulmonary artery. In our experience, and in that of others,[14] most neonates have not yet had a sufficient reduction in pulmonary resistance to allow reliable differentiation of systemic from pulmonary valve on the basis of systolic time intervals. Such intervals may be useful in older patients, however.

The suggestion that the posterior pulmonary artery in transposition may have a larger outside diameter than the anterior aorta[15] has not always been borne out in our experience. A possible reason for this may be the difficulty in obtaining a reliable measurement of the anterior aorta, if the valve is imaged with transducer angulation and not with the transducer perpendicular to the valve ring. Also, if pulmonary stenosis is present in transposition, the valve ring may be small.

With Doppler detection of patent ductus arteriosus and resultant identification of the pulmonary artery, we have been completely successful in separating infants with transposition from those without transposition. In using this method, the assumption is made that an anterior pulmonary artery, identified on the basis of receiving diastolic ductal flow, is not transposed. Such an assumption will be reasonable for the great majority of patients with transposition. We have not encountered the unusual defect of transposition with posterior aorta and anterior pulmonary artery reported in a series of four cases collected from Northern and Central America and Europe.[4] This rare form of transposition might not be correctly diagnosed on the basis of Doppler identification of the pulmonary artery.

Although real time two dimensional echocardiography has proved helpful in the evaluation of the course of great vessels,[17] and therefore in identifying the relation and course of transposed great vessels,[18] the expense of the equipment may limit its widespread application. Pulsed Doppler echocardiography equipment is less expensive and provides physiologic input into the great vessel diagnosis by identifying the pulmonary artery and screening for severe pulmonary hypertension and intracardiac defects that may not be detectable by other noninvasive means.

Methodologic considerations: As with any new technique, Doppler examinations must be performed with care, and a degree of initial experience is needed. Because the examination complements the more familiar A and M mode echocardiographic examinations, and because one knows at all times where blood flow characteristics are being evaluated, a knowledgeable M mode sonographer, familiar with the differential diagnostic possibilities in a given patient, should have relatively little difficulty. Indeed, detection of a patent ductus arteriosus from a precordial approach is one of the easiest and most dramatic of Doppler maneuvers.[3] Guided by the A and M mode scopes, and knowing the position of the great vessels, one follows the audio signal as the sample volume is moved through the ventricle and across the valve echo into the vessel. Regardless of the relation of the great vessels, the diastolic left to right ductal flows are from the aorta to the pulmonary artery and will therefore be directed toward a precordially placed transducer (Fig. 3). However, systolic flow from the ventricle to the pulmonary artery will be directed away from the transducer. Such directional differences are dramatically detected by Doppler study. In our experience, pulsed Doppler echocardiography is a reliable method for detecting and evaluating patent ductus arteriosus and has excellent sensitivity and specificity.[3,5]

Because the Doppler diagnosis of patent ductus arteriosus is based on the recording of diastolic ductal flow into the pulmonary artery, it is clear that the precordial Doppler approach described here will detect a patent ductus only when there is a left to right shunt component. Patients with patent ductus arteriosus and low pulmonary resistance characteristically have pandias-

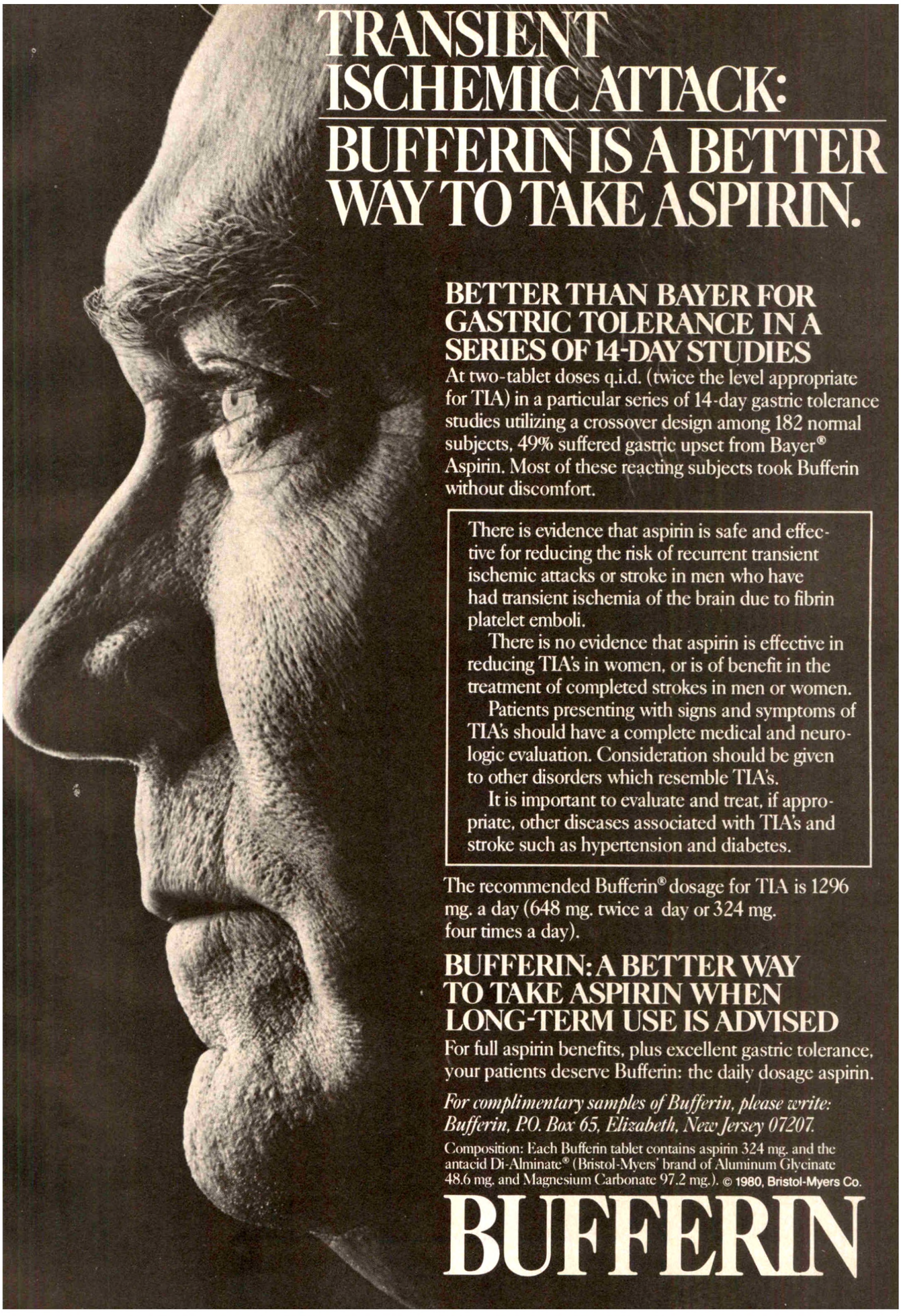
tolic ductal flow, whereas patients with marked pulmonary hypertension have a reduced duration of diastolic ductal flow.[5] If the pulmonary vascular resistance is much greater than systemic, as expected in severe cases of persistent fetal circulation syndrome, the ductal flow may be totally right to left, precluding detection of the ductus by the Doppler approach described here. In less severe cases of persistent fetal circulation syndrome, where some degree of bidirectional shunt may exist, we have been successful in detecting brief periods of diastolic ductal flow into the pulmonary artery.

Pulsed Doppler echocardiography versus cardiac catheterization: With basic Doppler experience, one should be able to detect patent ductus arteriosus and therefore identify the pulmonary artery. With the pulmonary artery identified, and evaluation of the connection attempted, one is still left with some patients who need cardiac catheterization. The value of pulsed Doppler echocardiography is in identifying those patients who do not need catheterization. Severely hypoxic, frequently acidotic infants are among those with the highest risk of death from catheterization. In many centers, catheterization is recommended for all infants whose response to added inspired oxygen is suboptimal and in whom congenital heart disease cannot be excluded. Our series contained 24 such patients with a questionable great vessel relation and M mode findings that did not exclude congenital heart disease. Transposition was correctly predicted or excluded with the Doppler study, thus materially aiding the decision on catheterization. Since our experience in pulsed Doppler techniques, there has been a marked decrease in the number of cyanotic neonates coming to catheterization but later proved to have a noncardiac cause of cyanosis. We usually do not recommend catheterization if M mode echographic and Doppler study identify two ventricles, two atrioventricular valves and two nontransposed great vessels, if there is no intracardiac blood flow abnormality (such as ventricular septal defect, pulmonary stenosis, massive tricuspid insufficiency) and if there are no findings suggestive of obstructed total anomalous pulmonary venous return (chest roentgenogram for vascular markings, right ventricular enlargement and pulmonary valve echographic findings of pulmonary hypertension, Doppler detected pulmonary valve insufficiency or abbreviated diastolic ductal flow).

In a 3 year experience, no patient with confirmed cyanotic heart disease has been denied a catheterization because of this policy. However, the Doppler definition of the pulmonary artery requires the presence of a patent ductus arteriosus. In the early neonatal period, this is not a significant limiting factor. But, with increasing postnatal age, the expected decrease in ductal prevalence may limit the application of the technique in older patients. We believe that pulsed Doppler echocardiography is a useful adjunct to ultrasonic evaluation of cyanotic newborns, its primary contribution being specific noninvasive definition of the pulmonary artery. Once the pulmonary artery is identified, the question of transposition may be answered.

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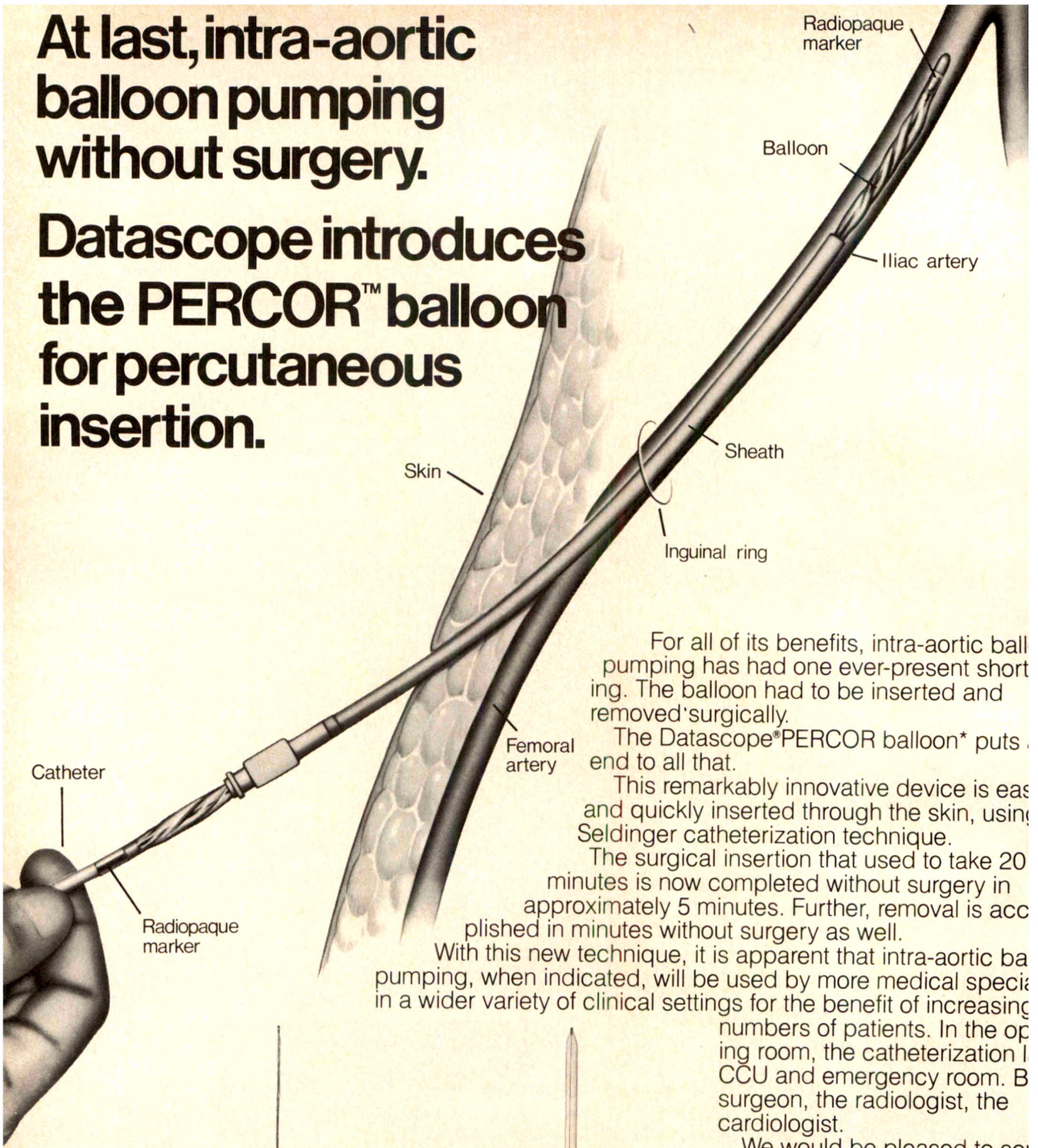
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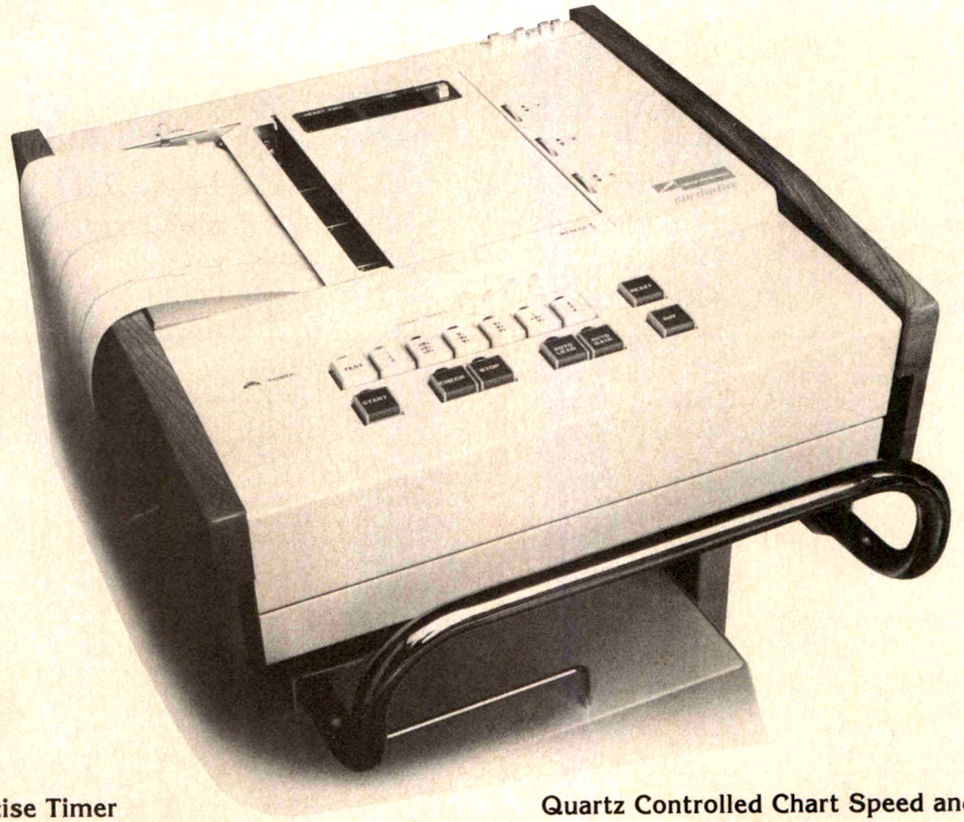


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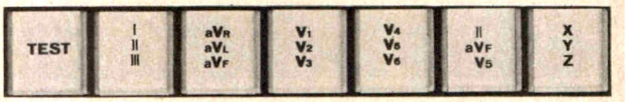


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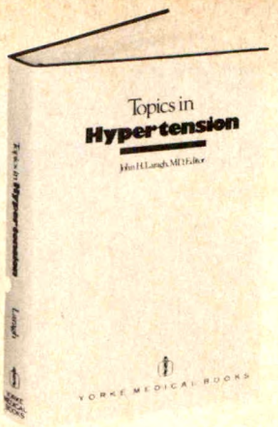
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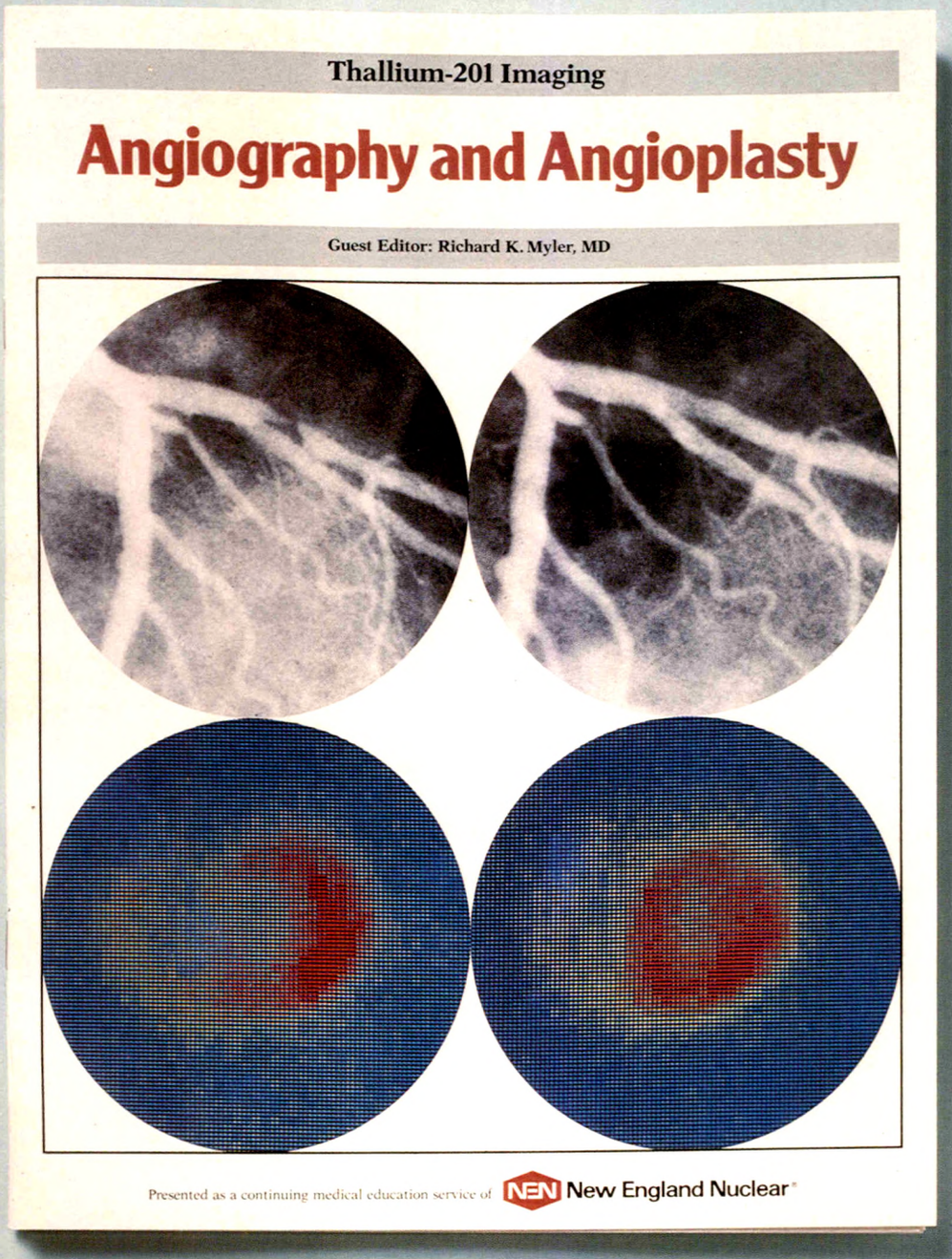
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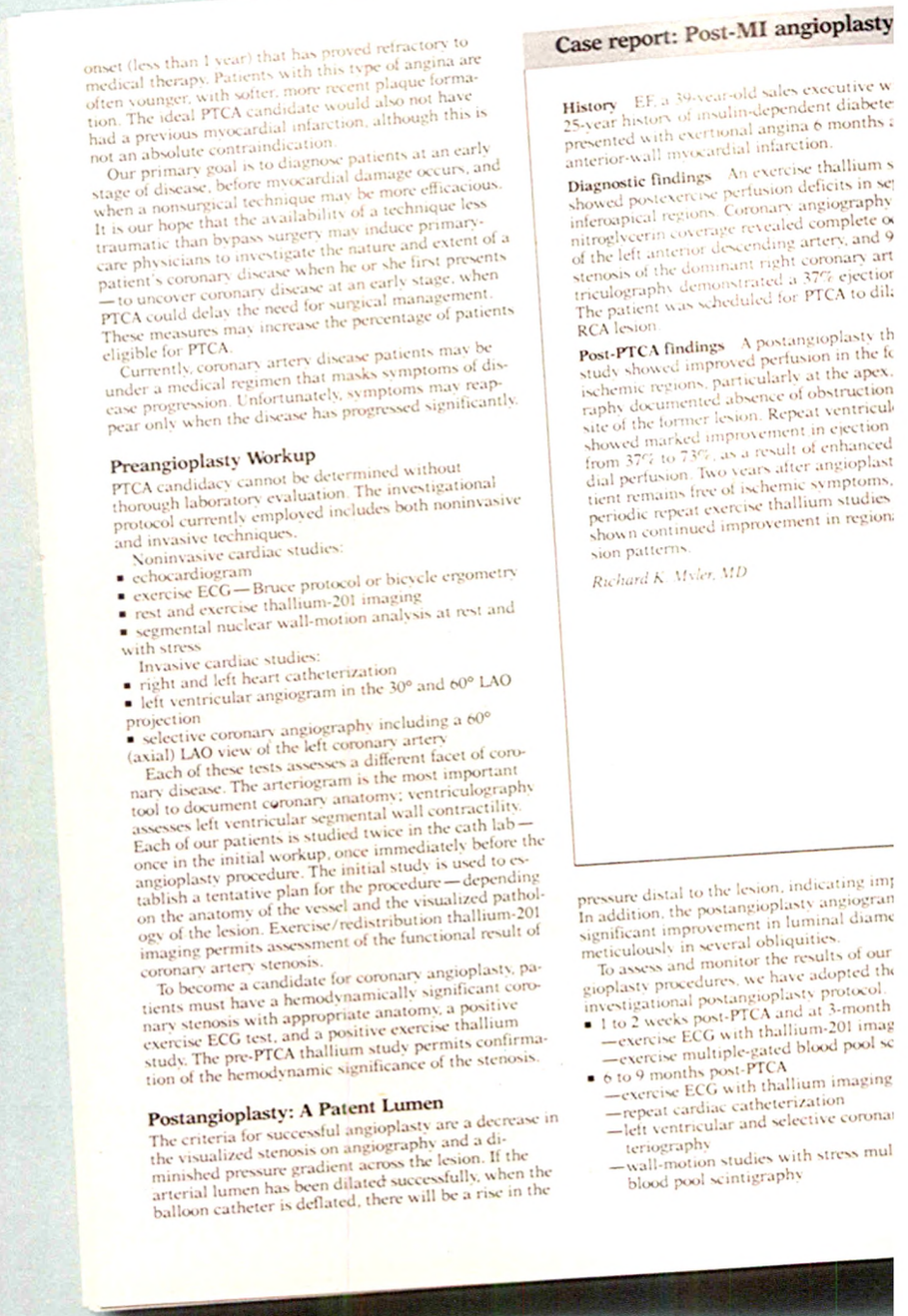
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As a practicing clinician, you've probably observed with growing interest the new diagnostic and therapeutic techniques for evaluating and managing your coronary artery disease patients. Two of the newest techniques entering routine clinical use hold great promise because they are relatively noninvasive: thallium-201 myocardial perfusion imaging, and percutaneous transluminal coronary angioplasty. Not surprisingly, the thallium-201 study has become a vital tool both in evaluation and followup of all patients being considered for angioplasty.



onset (less than 1 year) that has proved refractory to medical therapy. Patients with this type of angina are often younger, with softer, more recent plaque formation. The ideal PTCA candidate would also not have had a previous myocardial infarction, although this is not an absolute contraindication.

Our primary goal is to diagnose patients at an early stage of disease, before myocardial damage occurs, and when a nonsurgical technique may be more efficacious. It is our hope that the availability of a technique less traumatic than bypass surgery may induce primary-care physicians to investigate the nature and extent of a patient's coronary disease when he or she first presents —to uncover coronary disease at an early stage, when PTCA could delay the need for surgical management. These measures may increase the percentage of patients eligible for PTCA.

Currently, coronary artery disease patients may be under a medical regimen that masks symptoms of disease progression. Unfortunately, symptoms may reappear only when the disease has progressed significantly.

Preangioplasty Workup

PTCA candidacy cannot be determined without thorough laboratory evaluation. The investigational protocol currently employed includes both noninvasive and invasive techniques.

Noninvasive cardiac studies:

- echocardiogram
- exercise ECG—Bruce protocol or bicycle ergometry
- rest and exercise thallium-201 imaging
- segmental nuclear wall-motion analysis at rest and with stress

Invasive cardiac studies:

- right and left heart catheterization
- left ventricular angiogram in the 30° and 60° LAO projection
- selective coronary angiography including a 60° (axial) LAO view of the left coronary artery

Each of these tests assesses a different facet of coronary disease. The arteriogram is the most important tool to document coronary anatomy; ventriculography assesses left ventricular segmental wall contractility. Each of our patients is studied twice in the cath lab—once in the initial workup, once immediately before the angioplasty procedure. The initial study is used to establish a tentative plan for the procedure—depending on the anatomy of the vessel and the visualized pathology of the lesion. Exercise/redistribution thallium-201 imaging permits assessment of the functional result of coronary artery stenosis.

To become a candidate for coronary angioplasty, patients must have a hemodynamically significant coronary stenosis with appropriate anatomy, a positive exercise ECG test, and a positive exercise thallium study. The pre-PTCA thallium study permits confirmation of the hemodynamic significance of the stenosis.

Postangioplasty: A Patent Lumen

The criteria for successful angioplasty are a decrease in the visualized stenosis on angiography and a diminished pressure gradient across the lesion. If the arterial lumen has been dilated successfully, when the balloon catheter is deflated, there will be a rise in the

Case report: Post-MI angioplasty

History EF, a 39-year-old sales executive w
25-year history of insulin-dependent diabete
presented with exertional angina 6 months
anterior-wall myocardial infarction.

Diagnostic findings An exercise thallium s
showed postexercise perfusion deficits in se
inferoapical regions. Coronary angiography
nitroglycerin coverage revealed complete o
of the left anterior descending artery, and 9
stenosis of the dominant right coronary art
triculography demonstrated a 37% ejectior
The patient was scheduled for PTCA to dil
RCA lesion.

Post-PTCA findings A postangioplasty th
study showed improved perfusion in the fo
ischemic regions, particularly at the apex.
raphy documented absence of obstruction
site of the former lesion. Repeat ventricul
showed marked improvement in ejection
from 37% to 73%, as a result of enhanced
dial perfusion. Two years after angioplast
tient remains free of ischemic symptoms,
periodic repeat exercise thallium studies
shown continued improvement in region
sion patterns.

Richard K. Myler, MD

pressure distal to the lesion, indicating im
In addition, the postangioplasty angiogran
significant improvement in luminal diame
meticulously in several obliquities.

To assess and monitor the results of our
gioplasty procedures, we have adopted th
investigational postangioplasty protocol.

- 1 to 2 weeks post-PTCA and at 3-month
  —exercise ECG with thallium-201 imag
  —exercise multiple-gated blood pool sc
- 6 to 9 months post-PTCA
  —exercise ECG with thallium imaging
  —repeat cardiac catheterization
  —left ventricular and selective coronar
  teriography
  —wall-motion studies with stress mul
  blood pool scintigraphy

Contents:

Historical notes

Andreas R. Grüntzig, MD
University Hospital
Zurich, Switzerland

"Intraoperative experience demonstrated that coronary artery atheroma could be successfully compressed in the living human, and that disruption of the plaque produced no emboli."

Clinical indications and considerations

Richard K. Myler, MD
University of California,
San Francisco Medical School

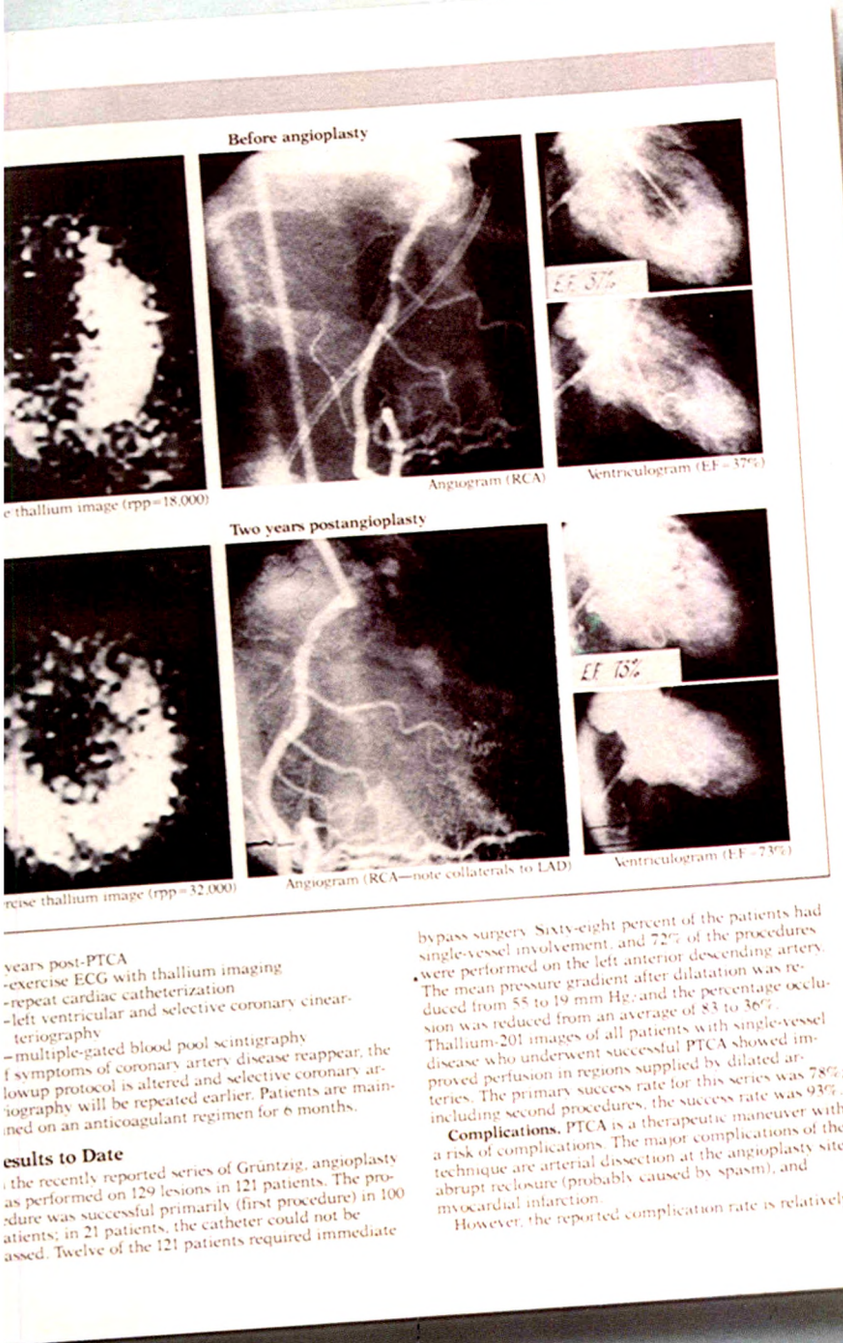
"Patients whose coronary artery disease responds to transluminal angioplasty typically present with severe angina... of recent onset... that has proved refractory to medical therapy."

A clinical primer on technique

Simon H. Stertzer, MD
Lenox Hill Hospital
New York, New York

"Whether the brachial or femora approach is used for the arterio raphy depends on the approach to be used for the angioplasty procedure and on the personal preference of the physician."

.and a new monograph on their synergy



years post-PTCA
-exercise ECG with thallium imaging
-repeat cardiac catheterization
-left ventricular and selective coronary cineariography
-multiple-gated blood pool scintigraphy
f symptoms of coronary artery disease reappear, the lowup protocol is altered and selective coronary arriography will be repeated earlier. Patients are mainined on an anticoagulant regimen for 6 months.

esults to Date

the recently reported series of Grüntzig, angioplasty as performed on 129 lesions in 121 patients. The produre was successful primarily (first procedure) in 100 atients; in 21 patients, the catheter could not be assed. Twelve of the 121 patients required immediate bypass surgery. Sixty-eight percent of the patients had single-vessel involvement, and 72% of the procedures were performed on the left anterior descending artery. The mean pressure gradient after dilatation was reduced from 55 to 19 mm Hg, and the percentage occlusion was reduced from an average of 83 to 36%. Thallium-201 images of all patients with single-vessel disease who underwent successful PTCA showed improved perfusion in regions supplied by dilated arteries. The primary success rate for this series was 78%; including second procedures, the success rate was 93%.

Complications. PTCA is a therapeutic maneuver with a risk of complications. The major complications of the technique are arterial dissection at the angioplasty site, abrupt reclosure (probably caused by spasm), and myocardial infarction.

However, the reported complication rate is relatively

allium-201 and angioplasty: ynergistic diagnostics

ndreas R. Grüntzig, MD
mon H. Stertzer, MD
th
artin E. Bloomfield, MD
nox Hill Hospital

allium imaging gives the ysician another measure of e hemodynamic significance an observed stenosis."

To assist clinicians in determining which of their patients might benefit from these new diagnostic and therapeutic techniques, New England Nuclear has underwritten the development of a new monograph on the synergy of thallium-201 imaging, angiography, and angioplasty. This monograph is available without charge upon request. Simply complete the reply card below and mail it for your copy. A slide program on the subject for teaching rounds use is also available.

☐ Please send me a complimentary copy of the *Angiography and Angioplasty* monograph.

☐ Please send me information on obtaining the *Angiography and Angioplasty* 35mm slide program for teaching rounds showings.

Name..... Title.....

Department.....

Institution.....

Institution address.....

City..... State..... Zip.....

Thallous Chloride Tl 201

FOR DIAGNOSTIC USE

DESCRIPTION: Thallous Chloride Tl 201 is supplied in isotonic solution as a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous administration. The aqueous solution at calibration time contains 1mCi/ml Thallous Chloride Tl 201, adjusted to pH 4.5-6.5 by the addition of hydrochloric acid and/or sodium hydroxide solution. It is made isotonic with 0.9% sodium chloride and is preserved with 0.9% benzyl alcohol. Thallium Tl 201 has a half-life of 73.1 hours and is cyclotron-produced. It is essentially carrier-free, and contains less than 0.25% lead Pb 203 and less than 1.9% Thallium Tl 202.

PHYSICAL CHARACTERISTICS

Thallium Tl 201 decays by electron capture to Mercury Hg 201 with a physical half-life of 73.1 hours.[1] Photons that are useful for detection and imaging are listed in Table 1. The lower energy X-rays obtained from the mercury Hg 201 daughter of Tl 201 are recommended for myocardial imaging, because the mean %/disintegration at 68-80.3 keV is much greater than the combination of gamma-4 and gamma-6 mean %/disintegration.

Table 1. Principal Radiation Emission Data

Radiation	Mean %/Disintegration	Mean Energy (keV)
Gamma-4	2.65	135.3
Gamma-6	10.0	167.4
Mercury X-rays	94.5	68-80.3

[1] Martin, M.J., Nuclear Data Project, ORNL, January 1977

EXTERNAL RADIATION

The specific gamma ray constant for Thallium Tl 201 is 4.7R/mCi-hr. at 1 cm. The first half-value layer is 0.23mm of lead. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead (Pb) is shown in Table 2. For example, the use of 3.3mm of lead will decrease the external radiation exposure by a factor of about 10,000.

Table 2. Radiation Attenuation By Lead Shielding

mm of Lead (Pb)	Coefficient of Attenuation
0.006	0.5
0.15	10^{-1}
0.98	10^{-2}
2.1	10^{-3}
3.3	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals before and after calibration are shown in Table 3.

Table 3. Thallium Tl 201 Decay Chart: Half-life 73.1 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-72	1.98	18	0.84	72	0.51
-60	1.77	24	0.80	78	0.48
-48	1.58	30	0.75	84	0.45
-36	1.41	36	0.71	90	0.43
-12	1.12	42	0.67	96	0.40
-6	1.06	48	0.63	108	0.36
0*	1.00	54	0.60	120	0.32
6	0.95	60	0.57	132	0.29
12	0.89	66	0.54	144	0.26

*Calibration Time

CLINICAL PHARMACOLOGY: Carrier-free Thallous Chloride Tl 201 has been found to accumulate in viable myocardium in a manner analogous to potassium. Experiments employing labeled microspheres in human volunteers have shown that the myocardial distribution of Thallous Chloride Tl 201 correlates well with regional perfusion.

In clinical studies, thallium images have been found to visualize areas of infarction confirmed by electrocardiographic and enzyme changes. Regions of transient myocardial ischemia corresponding to areas perfused by coronary arteries with partial stenoses have been visualized when thallium was administered in conjunction with an exercise stress test. It is usually not possible to differentiate recent from old myocardial infarction, and no exact differentiation can be made between recent myocardial infarction and ischemia.

After intravenous administration, Thallous Chloride Tl 201 clears rapidly from the blood with maximal concentration by normal myocardium occurring at about ten minutes.

INDICATIONS AND USAGE: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction.

It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products – especially those elective in nature – of women of childbearing capability should be performed during the first ten days following the onset of menses.

PRECAUTIONS: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

The expiration date for Thallous Chloride Tl 201 is six days postcalibration.

ADVERSE REACTIONS: Adverse reactions related to use of this agent have not been reported to date.

DOSAGE AND ADMINISTRATION: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

RADIATION DOSIMETRY

The estimated absorbed radiation dose[2] to an average patient (70kg) from an intravenous injection of a maximum dose of 1.5 millicuries of Tl 201 is shown in Table 4.

Table 4. Radiation Dose Estimates of Thallous Chloride Tl 201: Absorbed Dose/1.5mCi Thallium Tl 201 Administered

	Rads/1.5mCi
Heart	0.51
Small Intestines	0.97
Kidneys	2.2
Liver	0.93
Red Marrow	0.51
Ovaries	0.85
Testes	0.81
Thyroid	1.12
Total Body	0.36

[2] Values listed include a maximum correction of 13% to the radiation doses from Tl 201 due to the radiocontaminants Pb 203 and Tl 202

HOW SUPPLIED: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0 and 9.0 millicuries of Thallous Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

Catalog Number NRP-427 May 1980

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Attn: Teaching Program Administrator

Efficacy, Plasma Concentrations and Adverse Effects of A New Sustained Release Procainamide Preparation

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To assess the efficacy, plasma drug concentrations and adverse effects of a new sustained release preparation of procainamide, 33 patients with heart disease were studied in an acute dose-ranging protocol and a chronic treatment protocol. Patients initially received a daily dose of 3 g of sustained release procainamide; this dose was increased by 1.5 g daily until ventricular premature depolarizations were suppressed by 75 percent or more, adverse drug effects occurred or a total daily dose of 7.5 g of sustained-release procainamide was reached. Twenty-five patients (76 percent) had at least a 75 percent reduction (range 75 to 100 percent [mean ± standard deviation 91 ± 8.2]) in ventricular premature depolarization frequency at a dosage of 4.8 ± 1.46 g/day (range 3.0 to 7.5). Despite the 8 hour dosing interval, the variation between maximal and minimal plasma procainamide and N-acetylprocainamide concentrations under steady state conditions was very small. Mean maximal procainamide and N-acetylprocainamide plasma concentrations were 10.4 ± 6.02 and 12.0 ± 7.40 μg/ml, respectively. The respective mean minimal concentrations were 6.8 ± 4.50 and 8.7 ± 5.99 μg/ml. In nine patients (27 percent) treatment with sustained release procainamide resulted in conversion of the antinuclear antibody test from negative to positive. Adverse drug effects occurred in 17 (52 percent) of the subjects. In general, adverse effects were minor and abated within 24 hours after administration of the drug was stopped. One patient had the procainamide-induced systemic lupus erythematosus-like syndrome.

Procainamide is a versatile and effective antiarrhythmic agent that is commonly used to treat supraventricular and ventricular arrhythmias.[1–3] One factor that limits its usefulness is its relatively short half-life of elimination (3 to 6 hours). A rapid half-life of elimination necessitates frequent dosing to maintain therapeutic plasma concentrations, and thereby may contribute to poor patient compliance. To overcome this limitation, a new sustained release procainamide formulation was developed (Squibb Institute for Medical Research). Studies in normal volunteers show that this preparation is more slowly absorbed than are conventional procainamide capsules—consequently, under steady state conditions, plasma drug concentration is maintained longer after administration of a single dose. It is hoped that the increase in duration of action will improve patient compliance.

This study had three main goals: (1) to evaluate the efficacy of the new sustained release procainamide formulation in treatment of ventricular arrhythmia; (2) to determine the steady state plasma concentration of procainamide and N-acetylprocainamide after oral drug administration; and (3) to assess the incidence and nature of untoward drug-induced effects related to sustained release procainamide. To achieve the first two goals, we conducted an acute dose-ranging protocol. To achieve the third goal, we followed up the patients for up to 1 year.

From the Departments of Medicine and Pharmacology, College of Physicians and Surgeons, Columbia University, New York, New York and the Departments of Medicine and Pharmaceutical Sciences (Ruth E. Golding Clinical Pharmacokinetics Laboratory), Colleges of Medicine and Pharmacy, University of Arizona, Tucson, Arizona.
This study was supported in part by Grant HL-12738 from the U.S. Public Health Service, Bethesda, Maryland; Grants-in-Aid from the Chernow, Flinn and Winthrop Foundations, New York, New York; Grants RR-00645 and 3M01-RR00714 from the Research Resources Administration, Bethesda, Maryland and the Squibb Institute for Medical Research, Princeton, New Jersey. Manuscript received February 4, 1980; revised manuscript received April 14, 1980, accepted May 15, 1980.

* Research Fellowship Award, American Heart Association, Arizona Affiliate, Tucson, Arizona.
Address for reprints: J. Thomas Bigger, Jr., MD, 630 West 168th Street, New York, New York 10032.

Methods

Study patients: Patients with cardiac disease who had more than 10 ventricular premature depolarizations/hour were studied. All patients gave written informed consent before entering the protocol. Patients were enrolled in two centers, the Columbia-Presbyterian Medical Center and the University of Arizona Health Sciences Center. Each center conducted the same protocol. Before the study, each patient underwent the following procedures: history, physical examination, electrocardiography, chest X-ray examination, complete blood count, urinalysis, liver function tests, lupus erythematosus cell preparation, antinuclear antibody test, and determination of fasting blood sugar, serum creatinine and creatinine clearance, uric acid and calcium, phosphorus and cholesterol levels. Each test was repeated at the follow-up examinations and on withdrawal from the study. Administration of other antiarrhythmic drugs was discontinued at least 48 hours before entry into the study.

Acute dosing protocol: During each day of the acute dose-ranging protocol, patients had a 24 hour Holter electrocardiographic recording to assess heart rate and frequency of ventricular premature depolarizations. After a control 24 hour continuous electrocardiogram was obtained, dosing was started. The initial daily dosage was 3 g of sustained release procainamide (1 g every 8 hours). Each day, the dosage was increased by 1.5 g, (500 mg every 8 hours) until a 75 percen reduction in frequency of ventricular premature depolariza tions or adverse effects occurred or a total daily dosage of 7.5 g was given. The decision to increase the daily dosage wa made after a cardiologist had scanned the 24 hour electro cardiographic tapes on an Avionics Scanner (model 660A). A a later date, each Holter tape was analyzed using a digita computer program (Columbia IV). The mean rate (± standar deviation) of detection of ventricular premature depolariza tions with this program is 97 ± 6.1 percent and the false pos itive rate is 0.26 ± 0.35 percent.[4]

Chronic treatment protocol: The patients whose ven tricular premature depolarizations were reduced by 75 percen or more and who did not have adverse drug effects were can didates for the chronic treatment protocol. Under steady stat conditions, patients had plasma samples for procainamide and N-acetylprocainamide drawn 2, 4, 6 and 8 hours after the ef fective dose. Patients were discharged taking the effective dos and seen as outpatients 1, 3, 6, 9 and 12 months after dis charge. Outpatient visits included a history and physical ex amination by a cardiologist, plasma samples for procainamid and N-acetylprocainamide determination, a 24 hour Holte electrocardiographic recording, and routine blood tests tha included antinuclear antibody test and lupus erythematosu cell preparation. Patients were discharged from the chronic dosing protocol if they were noncompliant with the regimen

TABLE I

Clinical Characteristics of 33 Patients

Case	Age (yr) & Sex	Clinical Diagnosis	NYHA Class	Creatinine Clearance (ml/min)	Weight (kg)
1	49 M	UHD,NSH	IA	47	100
2	53 M	ASCVD,EH	IVD	21	55
3	61 M	CHD,EH	IIB	56	59
4	70 M	ASCVD,NSH	IIB	69	68
5	62 F	ASCVD,EH	IVD	29	60
6	69 M	ASCVD,EH	IIIC	40	58
7	53 F	UHD,EH	IIB	42	70
8	66 M	ASCVD,EH	IVD	64	85
9	64 M	ASCVD,NSH	IA	75	64
10	69 M	ASCVD,EH	IIIC	26	53
11	71 M	HCVD,EH	IIB	52	77
12	51 F	UHD,NSH	IA	58	58
13	74 M	ASCVD,EH	IIB	51	65
14	38 F	ASCVD,NSH	IA	56	114
15	55 F	ASCVD,EH	IIB	69	58
16	60 M	UHD,NSH	IA	60	68
17	32 F	UHD,NSH	IA	94	105
18	65 M	ASCVD,EH	IIB	65	114
19	35 F	CHD,NSH	IA	85	76
20	63 M	ASCVD,EH	IIB	71	88
21	71 M	ASCVD,NSH	IIB	35	76
22	38 M	UHD,NSH	IA	126	87
23	64 M	UHD,EH	IIB	45	81
24	46 M	UHD,NSH	IIB	85	60
25	70 M	ASCVD,EH	IIB	83	82
26	58 M	RHD,EH	IIB	84	86
27	61 M	ASCVD,NSH	IIB	100	74
28	64 M	HCVD,EH	IIB	60	81
29	50 M	ASCVD,NSH	IA	70	80
30	65 F	ASCVD,NSH	IIB	54	71
31	70 M	ASCVD,NSH	IIB	62	76
32	60 M	ASCVD,EH	IIB	70	80
33	62 F	HID,NSH	IA	102	68
Mean	59			64	76
± SD	11.2			23.1	15.9

ASCVD = arteriosclerotic heart disease; CHD = congenital heart disease; EH = enlarged heart; HCVD = hypertensive cardiovascular disease; HID = heart disease secondary to viral infection; NSH = normal size heart; NYHA Class = New York Heart Association functional classification; RHD = rheumatic heart disease; SD = standard deviation; UHD = unknown heart disease.

manifested adverse drug effects or died or if their primary physician considered that further treatment with the drug was not indicated.

Data analysis: Student's *t* test for paired samples was used to evaluate the statistical significance of the changes after drug treatment. Procainamide and N-acetylprocainamide determinations in plasma were measured with gas chromatography.[5] Procainamide and N-acetylprocainamide were reported as μg/ml base.

Results

Clinical features of patients: The 33 patients ranged in age from 32 to 74 years (mean ± standard deviation = 59 ± 11.2); 24 were men and 9 were women. All patients had heart disease: arteriosclerotic in 19, of unknown origin in 8, congenital in 2, hypertensive in 2, secondary to viral infection in 1 and of rheumatic origin in 1 (Table I). Twenty-eight patients were in New York Heart Association[6] functional class I or II, and five were in class III or IV. The 24 hour creatinine clearance ranged from 21 to 126 ml/min (mean 64 ± 23.1).

Eighteen patients (55 percent) were referred for treatment because they had not responded to one or more (up to six) of the following antiarrhythmic drugs: quinidine (12 patients); propranolol (6 patients); diphenylhydantoin (2 patients); disopyramide (1 patient); imipramine (1 patient); and mexiletine (1 patient).

Six patients (18 percent) had adverse drug effects associated with other antiarrhythmic agents: quinidine (gastrointestinal symptoms, four patients; thrombocytopenia, one patient; and hemolytic anemia, one patient); disopyramide (leg cramps and urinary retention, one patient); imipramine (hallucinations, one patient); and propranolol (depression, one patient).

Efficacy against ventricular arrhythmia: Holter electrocardiograms recorded during the control period ranged from 8 to 24 hours (mean 20 ± 3.4) and during the maximal efficacy period from 10 to 24 hours (mean 21 ± 2.9). There was no significant change in heart rate on these recordings. Heart rate during the control period ranged from 54 to 95 beats/min (75 ± 10.7) and at maximal efficacy from 46 to 84 beats/min (72 ± 9.7).

We used a 75 percent reduction in the 24 hour average ventricular premature depolarization count as the criterion of efficacy. Before treatment, the frequency of ventricular premature depolarizations/hour, ranged from 11 to 1,514 (mean 324 ± 359.9) (Table II). The

TABLE II

Effect of Sustained Release Procainamide on Ventricular Arrhythmia and Ventricular Coupling (R-V) Interval

	VPDs/hour		Episodes of Paired Complexes		Ventricular Tachycardia		R on T VPDs		R-V Interval (ms)	
Case	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	145	1	342	11	1	0	97	0	470	560
2	509	8	251	11	19	0	12	12	526	535
3	110	297	10	34	0	2	63	5	531	515
4	44	1	10	0	4	0	2	0	684	719
5	341	76	204	16	176	4	1	1	580	604
6	756	316	1853	0	861	0	8	0	587	584
7	323	20	87	1	21	0	150	0	480	517
8	494	36	727	22	164	3	199	7	587	584
9	11	1	0	0	0	0	19	0	487	552
10	69	0	31	0	1	0	2	0	486	521
11	16	2	3	0	2	0	18	0	461	510
12	28	1	6	0	0	0	259	1	527	608
13	64	5	22	0	0	0	227	0	458	615
14	751	143	114	15	2	0	0	0	489	509
15	1514	363	3899	194	811	15	397	0	519	537
16	601	552	230	7	2	0	4037	0	484	581
17	409	31	6	0	0	0	1374	0	373	526
18	529	8	13	0	0	0	3643	3	517	545
19	—	—	—	—	—	—	—	—	—	—
20	413	85	27	2	1	0	1	0	493	546
21	148	2	25	0	3	0	2	0	528	528
22	1273	98	8	4	0	0	224	6	464	511
23	—	—	—	—	—	—	—	—	—	—
24	172	4	240	0	3	0	0	13	439	442
25	63	1	7	0	1	0	7	0	572	535
26	55	4	14	2	4	1	689	0	491	673
27	321	65	186	13	8	0	0	0	539	506
28	187	26	238	1	1	0	5	1	621	646
29	17	5	0	1	0	0	0	0	594	639
30	290	38	0	0	0	0	3431	0	427	471
31	67	26	155	2	31	5	1	0	509	583
32	120	30	3	1	1	0	0	1	504	532
33	81	58	4	0	0	0	0	0	491	511
Mean	324	75	281	11	101	1	480	2	514	556
± SD	359.9	130.4	756.9	34.9	252.4	2.3	1110.2	3.4	62.0	59.4
Mean % improvement		82%		96%		99%		99%		
p		<0.001		<0.05		<0.025		<0.025		<0.001

p = probability; VPDs = ventricular premature depolarizations.

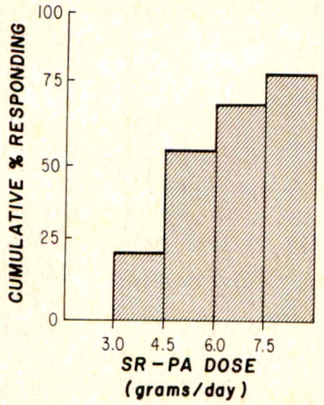


FIGURE 1. Cumulative percent of patients who responded to sustained release procainamide (SR-PA) with arrhythmic suppression (75 percent or more reduction in ventricular premature depolarizations) in relation to the effective dosage of the drug. Arrhythmia was suppressed in more than half of the patients with dosages of 3 to 4.5 g/day.

frequency at the conclusion of acute dose-ranging ranged from 0 to 552/hour (mean 75 ± 130.4) ($p < 0.001$). This represented 82 ± 24.1 percent improvement for the study group. Twenty-five (76 percent) of the 33 patients had at least a 75 percent reduction in ventricular premature depolarizations/hour (range 75 to 100 percent; mean 91 ± 8.2); 8 patients had a less than 75 percent reduction (Table II).

Sustained release procainamide was extremely potent against complex forms of ventricular arrhythmia. There was a 96 percent reduction in paired complexes, ($p < 0.05$) and a 99 percent reduction in episodes of ventricular tachycardia ($p < 0.025$) and in ventricular premature depolarizations with the R on T phenomenon ($p < 0.025$).

The average R-V interval of coupled ventricular premature depolarizations was determined for each patient before and after treatment with sustained release procainamide. The mean R-V interval was 514 ± 62.0 ms before treatment and 556 ± 59.4 ms after treatment ($p < 0.001$).

Plasma procainamide and N-acetylprocainamide concentrations: The dosage required to produce 75 percent improvement ranged from 3.0 to 7.5 (4.8 ± 1.46) g/day. More than one half of the patients responded to a dosage of less than 4.5 g/day (Fig. 1). The 25 patients who had a 75 percent or greater decrease in frequency of ventricular premature depolarizations were candidates for chronic treatment (see Methods). In 3 of the 25 patients (Cases 22, 24 and 27) adverse drug effects developed just before the start of chronic dosing, thereby precluding chronic drug administration. Therefore, 22 patients had procainamide and N-acetylprocainamide plasma concentrations determined (Table III). The mean maximal and minimal plasma procainamide concentration during a dosing interval under steady state conditions was 10.4 ± 6.02 and 6.8 ± 4.50 μg/ml, respectively. The mean maximal and minimal plasma N-acetylprocainamide concentration was 12.0 ± 7.40 and 8.7 ± 5.99 μg/ml, respectively. Despite the relatively long dosing interval of 8 hours, the

TABLE III

Maximal and Minimal Plasma Procainamide and N-acetylprocainamide Concentrations (μg/ml) in 22 Patients With Arrhythmic Suppression*

Case	Dosage (g/day)	Plasma Procainamide (μg/ml)		Plasma N-acetylprocainamide (μg/ml)	
		Max	Min	Max	Min
1	6.0	11.1	7.7	24.8	18.9
2	3.0	4.1	2.6	15.9	12.0
4	3.0	2.8	2.0	10.1	8.6
5	4.5	10.2	6.5	5.1	4.8
7	7.5	18.8	12.7	10.9	8.6
8	4.5	10.0	7.2	16.3	13.9
9	6.0	19.3	12.3	13.9	11.2
10	4.5	22.5	17.0	23.8	8.0
11	3.0	5.3	3.4	15.4	13.4
12	4.5	13.2	7.2	13.2	9.6
13	4.5	15.8	12.3	11.5	6.3
14	7.5	20.0	14.9	19.4	15.7
15	7.5	13.6	3.8	10.1	2.8
17	6.0	4.5	3.3	6.6	3.9
18	4.5	4.9	2.6	4.0	1.8
20	4.5	7.0	1.8	4.1	2.2
21	3.0	6.6	4.8	8.7	6.8
25	4.5	4.0	3.6	7.4	6.9
26	4.5	8.3	6.3	5.7	5.0
28	6.0	15.0	9.9	30.1	25.2
30	3.0	4.9	3.7	3.0	2.1
32	4.5	6.9	4.8	4.1	3.5
Mean	4.8	10.4	6.8	12.0	8.7
± SD	1.5	6.0	4.5	7.4	6.0

* Reduction of 75 percent or more in ventricular premature depolarizations.
Max = maximal; min = minimal.

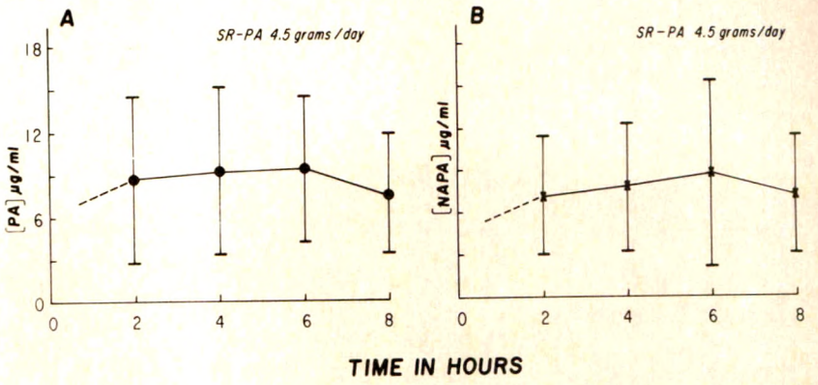


FIGURE 2. Time course of (**A**) plasma procainamide (PA) and (**B**) N-acetylprocainamide (NAPA) (mean ± standard deviation) in 10 patients who received sustained release procainamide (SR-PA), in a dosage of 4.5 g/day.

mean change in drug concentration was relatively small (3.6 ± 2.4 µg/ml for procainamide and 3.3 ± 3.3 µg/ml for N-acetylprocainamide). The procainamide and N-acetylprocainamide concentration varied by 43 and 35 percent, respectively. Thus, administration of sustained release procainamide results in very stable plasma drug concentrations over an 8 hour dosing interval.

This study was not designed to evaluate whether greater suppression of arrhythmia occurred in patients with high N-acetylprocainamide concentrations than in those with low concentrations. However, five patients had at least 75 percent suppression of arrhythmia when taking the minimal drug dosage (3 g/day) allowed by the protocol. Four of the five patients had N-acetylprocainamide concentrations two to four times greater than the procainamide concentrations. The high plasma N-acetylprocainamide concentrations in these patients raises the question whether N-acetylprocainamide contributed a greater antiarrhythmic effect than did procainamide.

To remove the variance due to different dosages, we plotted the mean and standard deviation of plasma procainamide and N-acetylprocainamide concentration in 10 patients who had greater than 75 percent reduction in ventricular premature depolarization frequency and received 4.5 g/day of sustained release procainamide (1.5 g every 8 hours) (Fig. 2). These patients represented the largest group who received the same dose. The drug concentration during 8 hour dosing interval was steady with little fluctuation. However, there was marked variability in the plasma drug concentration. As might be expected, patients who received large daily doses of sustained release procainamide generally had higher procainamide and N-acetylprocainamide plasma concentrations than did those receiving small daily doses (Fig. 3). However, even after dosage and body weight were considered, there still was substantial variability in plasma drug concentration.

Adverse effects and outcome: Seventeen patients (52 percent) manifested adverse drug effects (Table IV, Fig. 4). In nine patients these effects occurred during the acute dose-ranging protocol and in eight during chronic dosing.

The relation between the development of adverse effects from procainamide and slow acetylation phenotype has been raised by several investigators.[7,9] One method[7] of determining acetylation phenotype uses the

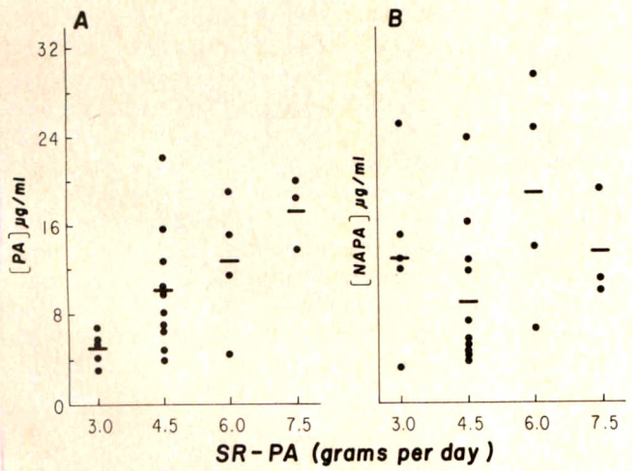


FIGURE 3. Maximal level of (**A**) plasma procainamide (PA) and (**B**) plasma N-acetylprocainamide (NAPA) and daily dosage. **Horizontal bars** designate the mean plasma concentration at the given dosage.

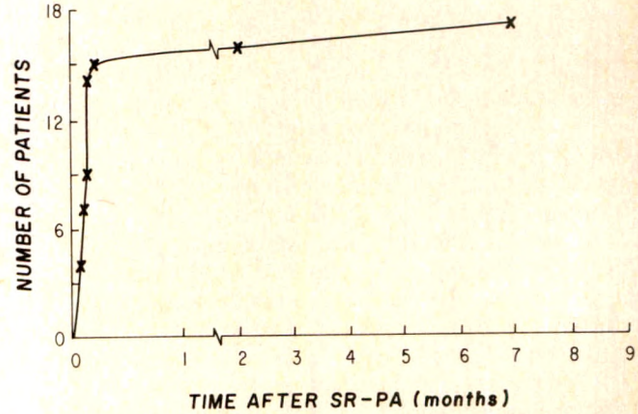


FIGURE 4. Cumulative number of patients who manifested adverse effects after receiving sustained release procainamide (SR-PA). Fifteen patients had adverse effects within the 1st week of the acute dose-ranging protocol and 2 and 7 months, respectively, after the start of chronic administration in two patients.

TABLE IV

Adverse Effects, Duration of Treatment With Sustained Release Procainamide and Result of Antinuclear Antibody Test After Treatment

Case	Nature of Adverse Effect	Duration of Treatment	Antinuclear Antibody Test After Treatment
1	Hypotension	5 days	Negative
3	Nausea, anorexia	3 days	Positive (1:20)
6	Nausea, dizziness	3 days	Positive (1:20)
8	Nausea, anorexia, headache	6 days	Positive (1:20)
9	Arthritis, + LE cell	7 months	Positive (1:20)
13	Rash	5 days	Negative
14	Nausea, vomiting	5 days	Negative
18	Headache, insomnia	2 months	Negative
19	Nausea, insomnia	4 days	Negative
22	Dizziness, headache	2 days	Negative
23	Nausea, ataxia	4 days	Negative
24	Dizziness, hallucinations	2 days	Negative
27	Weakness, fatigue, fever	2 days	Negative
28	Nausea, vomiting	5 days	Negative
29	Anorexia	5 days	Positive (1:20)
31	Anorexia, nausea, vomiting	2 days	. . .
33	Nausea, insomnia, fever	3 days	Positive (1:20)

LE = lupus erythematosus.

plasma N-acetylprocainamide/procainamide ratio in a plasma sample drawn 1.5 to 3 hours after a dose of procainamide. With this method, fast acetylators have a greater N-acetylprocainamide/procainamide ratio (greater then 0.95) than do slow acetylators (less than 0.85). Patients with a ratio between 0.85 and 0.95 have an indeterminate phenotype.

To observe the relation between acetylation phenotype and adverse effects and antinuclear antibody conversion, we determined acetylation phenotype using the plasma method.[7] Nine patients had antinuclear antibody conversion from negative to positive (Table II). Six patients had both adverse effects and a positive antinuclear antibody test. Their plasma N-acetylprocainamide/procainamide ratio ranged from 0.4 to 3.3 (mean 1.5 ± 1.31). Two patients had an N-acetylprocainamide:procainamide ratio of less than 0.85, indicating slow acetylation phenotype; two had a ratio of more than 0.95, indicating fast acetylation phenotype; one had a ratio of 0.88; and one had no plasma samples collected and, therefore, could not be classified. Three patients had no adverse effects but had antinuclear antibody conversion from negative to positive. The N-acetylprocainamide/procainamide ratio ranged from 0.5 to 3.5 (mean 1.5 ± 1.69) in this group. Two had an N-acetylprocainamide/procainamide ratio of less than 0.85, indicating slow acetylation phenotype and one had a ratio of more than 0.95, indicating fast acetylation phenotype. Our assessment of whether adverse effects and antinuclear antibody conversion are more frequent in slow than in fast acetylators after administration of sustained release procainamide was limited by the small number of patients who had adverse effects and a positive antinuclear antibody test and the variation in acetylation phenotype within the group.

Several subjects who had early adverse effects had high plasma procainamide and N-acetylprocainamide concentrations (*Table III*). The mean peak plasma procainamide and N-acetylprocainamide concentrations in patients who had adverse effects were 13.7 ± 5.4 and 17.1 ± 8.6 μg/ml, respectively; in patients who did not have adverse effects the values were 8.8 ± 5.8 and 9.6 ± 5.6 μg/ml. The mean dosage for the patients with and without adverse effects did not differ (4.7 ± 1.7 versus 4.5 ± 1.5 g/day).

Nature of adverse effects: Symptoms that necessitated withdrawal from the protocol were uncomfortable and annoying, but generally disappeared within 8 to 24 hours after drug administration was discontinued. Gastrointestinal complaints occurred in 10 patients, neurologic disturbances in 8, weakness or fatigue in 2, drug-induced fever in 2, rash in 1 and postural hypotension in 1. In one patient (Case 9) the procainamide-induced systemic lupus erythematosus-like syndrome developed. This patient was discharged taking 6 g/day and after 7 months had migratory arthralgias and a positive (1:20) antinuclear antibody test and lupus erythematosus cell preparation. Symptoms, antinuclear antibody test and lupus erythematosus cell preparation returned to normal 1 month after discontinuation of the drug administration. This patient had taken three other antiarrhythmic drugs in the past, but had adverse effects from each of them as well. Quinidine had caused thrombocytopenia requiring three blood transfusions; he became agitated with imipramine and depressed with propranolol.

Discussion

Variation in plasma blood levels: The relatively short half-life of elimination of conventional procain-

amide (3 to 6 hours) requires frequent dosing to maintain plasma procainamide and N-acetylprocainamide concentrations within the therapeutic plasma drug concentration range.[2,3] To circumvent this limitation of an otherwise effective antiarrhythmic agent, a new sustained release formulation of procainamide has been developed. Because this formulation prolongs the rate of absorption of procainamide, plasma drug concentrations tend to fluctuate less over the dosing interval.

There are reports on the kinetics of two other procainamide preparations that prolong absorption and are available in Europe.[10–12] Both of these other two slow-release formulations have been reported to produce fewer daily fluctuations than those produced by conventional procainamide. In this study, we evaluated the sustained release procainamide formulation prepared by the Squibb Institute for Medical Research. No other studies of this new formulation are now available in the United States. The difference between the mean maximal and minimal procainamide concentrations was 3.6 ± 2.4 μg/ml and between the mean maximal and minimal N-acetylprocainamide concentration was 3.3 ± 3.3 μg/ml. Thus, the variation in plasma drug concentration with this new formulation is slight during an 8 hour dosing interval. There was wide variability in plasma procainamide and N-acetylprocainamide concentrations among the patients studied. Different rates of gastrointestinal absorption of the sustained release preparation, variable rates and extent of metabolism of procainamide to N-acetylprocainamide, diminished renal function or an altered volume of distribution in patients with heart disease could account for the variability observed. Further studies are indicated in order to evaluate which of these factors are most important.

Many patients who had early adverse drug effects had high plasma procainamide and N-acetylprocainamide concentrations. If drug concentrations can be determined in patients who are likely to attain such high levels, it is possible that adverse effects will be minimized. Patients with severe heart failure and those with decreased renal function are likely to achieve higher plasma concentrations than normal subjects. Such patients will probably reach effective plasma drug concentrations with smaller doses and maintain effective concentrations with longer dosing intervals (every 12 hours).

Antiarrhythmic efficacy: Sustained release procainamide is an effective antiarrhythmic agent as evidenced by greater than 90 percent suppression of ventricular premature depolarizations in 76 percent of patients. Moreover, this agent is very potent against complex forms of ventricular arrhythmia (paired complexes, ventricular tachycardia and ventricular premature depolarizations with the R on T phenomenon). Giardina and Bigger[13] showed that procainamide increases the R-V interval of coupled ventricular premature depolarizations as it decreases their frequency. They postulated that prolongation of the coupling interval accounts for the mechanism of action of procainamide against reentrant arrhythmia; that is, procainamide further depresses conduction in the reentrant loop. The striking increase in the R-V interval and the decrease in R on T ventricular premature depolarizations seen in our study with sustained release procainamide reaffirms the observation made with procainamide in 1973.

Early and late adverse effects: A total of 15 patients (45 percent) had adverse effects during the 1st week of the study. Only two patients followed up during the chronic dosing protocol had late adverse effects—at 2 and 7 months, respectively. These results contrast with the report of Kosowsky et al.,[14] who followed up 39 patients taking conventional procainamide for prophylaxis against arrhythmia after acute myocardial infarction. In that study, 9 (23 percent) of 39 patients had early adverse effects (within 3 weeks) and 14 (87 percent) of 16 patients had late adverse effects. In our study, 45 percent of the patients had early adverse effects whereas only 12 percent (2 of 17) of patients followed up for 1 month to 1 year had late adverse effects. Thus, it is possible that the incidence of late adverse effects with sustained release procainamide differs from that of conventional procainamide. We do not know whether more patients would have had adverse effects if they had been followed up for more than 1 year.

Therapeutic implications: Our results indicate that sustained release procainamide is a potent antiarrhythmic agent. This is noteworthy because 55 percent of the patients had had no suppression of arrhythmia with other antiarrhythmic drugs. Most of the adverse effects appeared early and there was a relation between high procainamide and N-acetylprocainamide plasma concentrations and untoward drug effects. If adverse effects can be limited during acute dose-ranging, the effectiveness of sustained release procainamide in suppressing ventricular arrhythmia, particularly ventricular premature depolarizations with complex features, should make it a useful antiarrhythmic agent. In addition, the steady plasma drug concentrations attained with the new formulation allow a longer dosing interval, which is a significant improvement over conventional procainamide.

Acknowledgment

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Further Insights Into Digoxin-Quinidine Interaction: Lack of Correlation Between Serum Digoxin Concentration and Inotropic State of the Heart

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The digoxin-quinidine interaction was studied in nine healthy human subjects aged 26 to 31 years. A single oral dose (400 mg) of quinidine sulfate administered to subjects taking digoxin resulted in a mean (± standard error of the mean) increase within 1 to 6 hours in the serum digoxin concentration of 0.12 ± 0.01 ng/ml ($p < 0.0001$), an increase of 21 percent. Continued quinidine administration for 24 hours resulted in a 59 percent increase in the mean serum digoxin concentration from 0.68 ± 0.04 to 1.04 ± 0.06 ng/ml (alpha = 0.05). At the same time, however, systolic time intervals demonstrated a lengthening of the mean left ventricular ejection time index from 406 ± 4 to 419 ± 2 ms (alpha = 0.05) and the mean Q-S_2 index from 524 ± 6 to 532 ± 7 ms (difference not significant [NS]). When compared with the shortening of these intervals predicted from the digoxin dose-response curve if digoxin were the only variable, the lengthening actually observed for both intervals was highly significant. The negative inotropic effect of quinidine administration alone was assessed with systolic time intervals in four subjects. The left ventricular ejection time index lengthened from 419 ± 3 to 425 ± 6 ms (NS) and the Q-S_2 index from 541 ± 6 to 550 ± 7 ms (NS). Therefore, the lengthening of these intervals in subjects taking digitalis after the addition of quinidine represents more than just the negative inotropic effect of quinidine, and occurs despite the increase in serum digoxin concentration.

The results of this study support the view that quinidine displaces digoxin from tissue-binding sites as a major mechanism of the interaction. Furthermore, it appears that quinidine may specifically displace digoxin from cardiac-binding sites. These results raise important questions concerning the recommendation to reduce the maintenance digoxin dose when concomitant quinidine therapy is initiated.

Since 1977, many reports[1–7] have documented that in patients taking digoxin the serum concentration of this agent increases when quinidine is added to the regimen. In a recent editorial review on the subject, Bigger[8] emphasized that several important questions remain unanswered. First, what is the early time course of the digoxin-quinidine interaction? Several reports[9,10] have suggested that the increase in the serum digoxin concentration begins on the 1st day of quinidine administration and rises to a new steady state level in about 5 days. However, the precise effect of quinidine on digoxin levels during the first 24 hours of quinidine administration remains undefined.

Second, is there an inotropic concomitant of the increased serum digoxin concentration that results from the addition of quinidine to the therapeutic regimen? There have been reports[3] that subjective adverse gastrointestinal symptoms (nausea, vomiting and anorexia) occur in association with the increase in serum digoxin concentrations resulting from simultaneous quinidine administration. There has also been some

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effort to correlate the fluctuations in serum digoxin concentrations under these circumstances with changing electrocardiographic patterns and cardiac rhythms.[10] However, although some effort has been made to examine objective signs suggesting increased digoxin effects on the heart, very few systematic studies of this issue have been made in a prospective fashion. There are at least several theoretical reasons why one might not necessarily expect an increase in serum digoxin concentration resulting from a digoxin-quinidine interaction to reflect itself in an enhanced cardiac digoxin effect. These reservations were well outlined by Bigger.[8]

Therefore, we undertook this study (1) to investigate the early time course of the digoxin-quinidine interaction, and (2) to document in prospective fashion any inotropic influence of the digoxin-quinidine interaction. Additionally, we hoped that answers to these two questions might shed further light on the mechanism of this interaction.

Methods

Subjects: Nine healthy volunteers (including eight house staff physicians), six men and three women aged 26 to 31 years, gave written informed consent for participation in this study. The subjects were instructed to not take any prescribed or over-the-counter medications and to refrain from any alcohol consumption during the study. Two of the women continued to take oral contraceptive agents. No subject was a cigarette smoker. Each underwent a normal baseline physical examination, complete blood count, blood chemistry determinations and electrocardiogram.

Procedure: The subjects took digoxin (Lanoxin®, Burroughs Wellcome), 0.25 mg orally, at 10 p.m. for 7 days. On day 7, each took quinidine sulfate, 400 mg orally, at 8 a.m. Seven subjects completed the next portion of the protocol by taking quinidine sulfate, 400 mg every 6 hours, for a total of four doses (day 7). The study was terminated in two who did not complete the regimen because of nausea and lightheadedness after the first dose of quinidine.

On day 1, systolic time intervals were recorded at 8 a.m. On day 6, systolic time intervals were recorded at 8 a.m., and the serum digoxin concentration was determined at this time and at 9 a.m., 10 a.m., 12 noon and 2 p.m. On day 7, quinidine sulfate was taken after serum digoxin concentration was measured at 8 a.m. Then at 9 a.m., 10 a.m., 12 noon and 2 p.m. both serum digoxin and quinidine concentrations were measured. At 8 a.m. on day 8, systolic time intervals were recorded and serum digoxin and quinidine concentrations measured. Twelve lead electrocardiograms were taken on days 6 and 8 to exclude arrhythmia and assure safe QRS and Q-T intervals.

After 1 week without any medications, four of the subjects volunteered to take quinidine sulfate, 400 mg orally, every 6 hours for a total of four doses, starting at 8 a.m. Systolic time intervals were recorded at 8 a.m. immediately before and again at 8 a.m. immediately after the 24 hours of quinidine administration.

Systolic time intervals: An Irex Continutrace 101 Recorder was used to simultaneously record the phonocardiogram, a lead II electrocardiogram and an indirect carotid pulse tracing at a paper speed of 100 mm/s. The left ventricular ejection time (LVET) was measured from the point of initial rapid upstroke of the carotid pulse tracing to the dicrotic notch. The Q-S_2 interval was measured from the beginning of the first deflection of the QRS complex to the initial high frequency component of the second heart sound. The latter was obtained with an appropriate frequency filter in the aortic region. The LVET and Q-S_2 intervals were indexed for heart rate based on the formulas of Weissler et al.[11,12]: LVET index = LVET + 0.0016 × (heart rate); Q-S_2 index = Q-S_2 + 0.002 × (heart rate). Systolic time intervals were measured in a blind fashion without knowledge of the patient's drug regimen by one of us (P.H.). There were no significant differences in measurements by an independent blinded observer who reviewed random tracings.

Laboratory techniques: Serum digoxin concentrations were determined with Corning's ImmoPhase Digoxin ^{125}I Radioimmunoassay Test System (Medfield, Massachusetts). Serum quinidine concentrations were determined with the fluorometric method of Brodie and Udenfriend.[13]

Statistical analysis: A single factor repeated measures analysis of variance[14] was used to test for a difference in serum digoxin concentrations at 8 a.m. on days 6, 7, and 8. With establishment of a significant day effect ($p < 0.0001$), specific comparisons were performed using the Newman-Keuls multiple comparison procedure[14] testing the difference among the three serum digoxin concentrations at the alpha = 0.05 level. An analysis of variance with repeated measures on two factors[15] (day and time of day) was used to test for a day difference between the serum digoxin concentrations obtained at 8, 9 and 10 a.m., 12 noon and 2 p.m. on days 6 and 7.

The Q-S_2 index and left ventricular ejection time index were tested for differences among treatment conditions (baseline, digoxin, digoxin plus quinidine and quinidine alone) by the single factor repeated measures analysis of variance procedure. After a significant treatment effect for both intervals was established ($p < 0.001$), the Newman-Keuls multiple comparison procedure was used to test the differences for each of the intervals among the various treatment conditions at the alpha = 0.05 significance level. All data are given as the group mean ± standard error of the mean.

Results

Subjects were studied under four conditions: (1) baseline, (2) digoxin alone, (3) digoxin plus quinidine, and (4) quindine alone. Under each of these experimental conditions, two variables were measured: (1) serum digoxin concentrations, and (2) systolic time intervals. The systolic time intervals obtained in the baseline condition in this study yielded a mean left ventricular ejection time index and mean Q-S_2 index that were almost identical to those reported by other investigators[16,17] in healthy human subjects of similar age, thus suggesting satisfactory reproducibility.

Effects of digoxin alone: All nine subjects took maintenance oral doses of digoxin for 7 days. By day 6, a steady state with respect to digoxin had been achieved as evidenced by the lack of significant difference between the mean serum digoxin concentrations obtained at 8 a.m. on days 6 and 7 (0.63 ± 0.07 and 0.68 ± 0.04 ng/ml, respectively) (Fig. 1). Comparison of systolic time intervals obtained on day 6 of digoxin administration with those obtained in the baseline state revealed a significant reduction (alpha = 0.05) in the mean left ventricular ejection time index from 419 ± 3 to 406 ± 4 ms (Fig. 2) and mean Q-S_2 index from 541 ± 6 to 524 ± 6 ms (Fig. 3).

Effects of digoxin plus quinidine: After the first dose of oral quinidine sulfate, there was a small but significant increase in the serum digoxin concentrations ($p < 0.0001$) over the ensuing 1 to 6 hours compared with control values obtained on the previous day (Fig. 1). The mean peak serum quinidine level after the single 400 mg dose was 2.8 ± 0.34 mg/liter.

After a total of four doses of quinidine over a 24 hour interval during continued maintenance digoxin administration, there was an increase in the mean serum digoxin concentration obtained at 8 a.m. on day 8 to 1.04 ± 0.06 ng/ml, a 59 percent increase over that of the day before quinidine administration (alpha = 0.05). The mean serum quinidine level at that time was 3.9 ± 0.25 mg/liter.

Systolic time intervals measured at the same time (8 a.m., day 8) when compared with those measured during administration of digoxin alone revealed a lengthening of the mean left ventricular ejection time index from 406 ± 4 to 419 ± 2 ms (Fig. 2) and the mean Q-S_2 index from 524 ± 6 to 532 ± 7 ms (Fig. 3). At the alpha = 0.05 level, this lengthening was significant for the former but not for the latter index.

Effects of quinidine alone: When quinidine was readministered in the same dosages for 24 hours to four subjects after 1 week without any medication, there was a small but not statistically significant lengthening of the mean left ventricular ejection time index from 419 ± 3 to 425 ± 6 ms (Fig. 2) and of the mean Q-S_2 index from 541 ± 6 to 550 ± 7 ms (Fig. 3) compared with baseline values.

Discussion

Several investigators[1,2,4–6] reported almost simultaneously in 1977 and 1978 a similar observation made in their independent laboratories. They each noted that when quinidine was given to patients on a long-term stable digoxin regimen, the serum digoxin concentration increased significantly. We undertook this study to determine the answers to two still unresolved questions concerning the digoxin-quinidine interaction.

1. What is the early time course of the digoxin-quinidine interaction?: When steady state serum digoxin concentrations were reached after 6 days of maintenance digoxin administration, we found that a single dose of quinidine sulfate increased the mean serum digoxin concentration over the next 1 to 6 hours

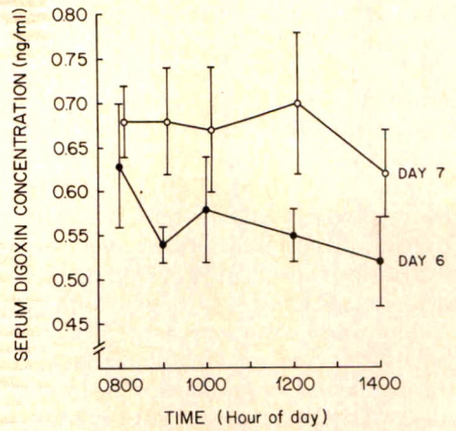


FIGURE 1. Mean (± standard error of the mean) serum digoxin concentrations for nine subjects before (DAY 6) and after (DAY 7) administration of quinidine sulfate, 400 mg orally, given at 8 a.m. (0800) on day 7. The 8 a.m. values are not statistically different, indicating a steady state for serum digoxin concentration. Curves for days 6 and 7 are different ($p < 0.0001$).

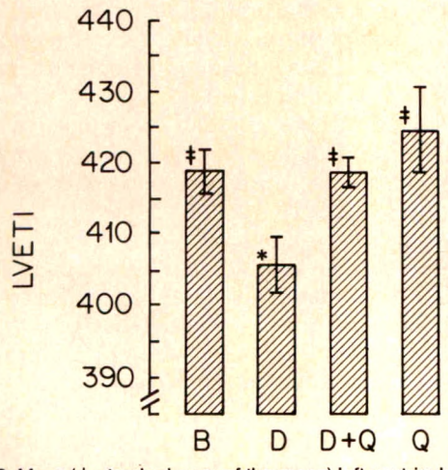


FIGURE 2. Mean (± standard error of the mean) left ventricular ejection time index (LVETI) measured in milliseconds under four conditions. Values marked with a **double dagger** (‡) are similar to each other, but statistically different from that marked with an **asterisk** (*) (alpha = 0.05). B = baseline; D = steady state digoxin; D + Q = steady state digoxin plus 24 hours of quinidine; Q = 24 hours of quinidine alone.

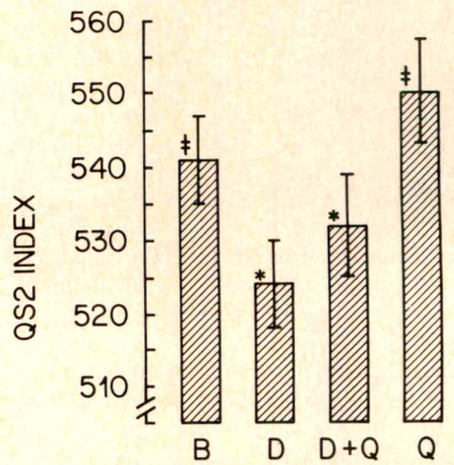


FIGURE 3. Mean (± standard error of the mean) Q-S_2 index measured in milliseconds under four conditions. Values marked with a **double dagger** (‡) are similar to each other. Values marked with an **asterisk** (*) are similar to each other. ‡ and * values are different at the alpha = 0.05 level. Abbreviations as in Figure 2.

slightly but significantly when compared with control values obtained with digoxin alone ($p < 0.0001$). After continued quinidine and digoxin administration, the mean serum digoxin concentration continued to increase to 59 percent above the steady state control value obtained before quinidine administration (alpha = 0.05).

2. Is there any inotropic effect of the increase in serum digoxin concentration that results from the digoxin-quinidine interaction?: We used systolic time intervals to assess changes in the inotropic state of the heart. Weissler and his co-workers[16,18] demonstrated the usefulness of systolic time intervals as a method for providing a quantitative measure of the inotropic effect of digitalis glycosides in normal subjects. These investigators concluded that the $Q\text{-}S_2$ index is the most sensitive of the systolic time intervals in this regard because it incorporates the shortening effect of digitalis on both the left ventricular preejection period and ejection time. The $Q\text{-}S_2$ index is a measure of the total time of electromechanical systole normalized for heart rate. The left ventricular ejection time index is also useful because it is an expression of the duration of ventricular ejection normalized for heart rate. After digitalis administration to normal subjects, there is a shortening of this index, reflecting the enhanced mean rate of left ventricular ejection due to digitalis. Although other systolic time intervals may have also proved useful, we selected the $Q\text{-}S_2$ index and left ventricular ejection time index for evaluation on the basis of the results of these studies. We confirmed the findings of Weissler and his collaborators in that the inotropic effect of digoxin was reflected by a significant shortening of both these systolic time intervals.

As shown by Hoeschen and Cuddy,[19] who used systolic time intervals to study the digoxin dose-response curve in healthy human subjects, the serum digoxin concentrations obtained with digitalization in our study were well within the steep portion of the dose-response curve. If digoxin were the only variable, the observed increase in the mean serum digoxin concentration from 0.68 ± 0.04 to 1.04 ± 0.06 ng/ml would have been expected to result in a further significant increase in the inotropic state of the heart as reflected by shortening of the $Q\text{-}S_2$ and left ventricular ejection time indexes. However, despite this 59 percent increase in the mean serum digoxin concentration after 24 hours of quinidine administration to subjects taking digoxin, the systolic time intervals documented a reduction from the previously enhanced inotropic state of the heart.

Is this merely a reflection of the primary negative inotropic effect of quinidine? Our results suggest it is more than this. As a control, we measured the effect of 24 hours of quinidine administration alone on the systolic time intervals. There was a small but not statistically significant lengthening of the mean $Q\text{-}S_2$ and mean left ventricular ejection time indexes over baseline values, reflecting a small negative inotropic effect of quinidine in healthy human subjects. However, when quinidine was added to digoxin there was a marked lengthening of these systolic time intervals compared with the values that would have been predicted on the basis of the digoxin dose-response curve. This finding suggests a secondary reduction in the inotropic effect of digoxin in the presence of quinidine, in addition to a primary reduction in the inotropic state due to quinidine itself. It could still be argued that quinidine might simply exert a greater negative inotropic effect on the digitalized myocardium than on the nondigitalized myocardium. This explanation is unlikely, but it has not been excluded by our study.

Mechanism of the interaction: The mechanism of the digoxin-quinidine interaction remains in dispute. It has been suggested that several mechanisms may be operative. Leahey et al.[3] and Ejvinsson[4] postulated that quinidine displaced digoxin from tissue-binding sites. In support of this theory, Straub et al.[20] reported that high concentrations of quinidine displaced digoxin from beef heart adenosine triphosphatase preparations. However, Doering[9] found no evidence that quinidine displaced digoxin from the sarcolemmal fraction of lamb myocardium. More recently, Doherty et al.[21] presented further data to confirm the tissue displacement hypothesis. After the administration of quinidine to digitalized dogs, these investigators observed a 20 to 25 percent reduction in tritiated digoxin content of heart and skeletal muscle, with a greater than 50 percent increase in brain content of digoxin. Quinidine, therefore, resulted in redistribution of digoxin in major tissue depots.

Hager et al.[22] presented additional pharmacokinetic data to support the notion of displacement. Their data suggest a decrease in the volume of distribution for digoxin as a result of quinidine administration. Because clearance = (volume of distribution) × (rate constant of elimination), a reduction in the volume of distribution of digoxin after quinidine administration implies a reduction in clearance of digoxin at the same time. Several reports[5,9,22,23] have indeed shown a reduced renal clearance of digoxin after quinidine administration. If administration of quinidine does lead to a diminution in the volume of distribution for digoxin, it may well be as a result of displacement of digoxin from tissue-binding sites. Our results tend to support the theory that quinidine displaces digoxin from tissue-binding sites and, more specifically, displaces it from cardiac-binding sites.

To add to the confusion, Chen and Friedman[24] recently presented an abstract of their findings in human subjects. They concluded that enhanced gastrointestinal absorption of digoxin occurs when oral digoxin is administered simultaneously with oral quinidine. We observed in our investigation a significant increase in serum digoxin concentrations within 1 to 6 hours after a single oral quinidine dose that was administered fully 10 hours after the last digoxin dose had been given. Four doses of quinidine were given over a 24 hour period in our study—2, 4, 8 and 10 hours, respectively, from the nearest digoxin dose—during which time the serum digoxin concentration increased by 59 percent. We be-

lieve that enhanced gastrointestinal absorption is highly unlikely to be a significant contributing factor to our results.

Therapeutic implications: Recently, investigators[8,9] have recommended decreasing the maintenance digoxin dose by one-half when instituting simultaneous quinidine therapy. This recommendation is based on scanty objective data and is primarily the result of a theoretical concern over the increase in the serum digoxin concentration. Smith and co-workers[25–27] showed a correlation between serum digoxin concentration and digitalis intoxication, but their studies also demonstrated a fair degree of overlap of serum digoxin concentrations in patients with and without clinical toxicity. Ingelfinger and Goldman[28] pointed out in 1976 that the usefulness of the serum digoxin concentration as a test for digitalis toxicity had not been established. Lasagna[29] further argued that the serum digoxin concentration may not at all times and in all situations, even within the same subject, match the concentration of the drug at the receptor site of interest. This effect is most apparent clinically when digoxin-specific antibodies are used to treat digoxin toxicity. Despite huge increases in the serum digoxin concentration after administration of Fab fragments, the myocardial concentration and effects of digoxin are reduced.[30] If the digoxin dosage is decreased when quinidine is added to a patient's regimen, the reduced inotropic effect of digoxin demonstrated in our study will be attenuated even further.

There are three possible alternative relations of the inotropic and toxic effects of digoxin. First, if the mechanism of digoxin cardiac toxicity is unrelated to the mechanism of its inotropic effect, then the recommendation to decrease the digoxin dose when quinidine therapy is added may still be indicated in order to avoid toxicity. However, if the toxic and inotropic effects are primarily related, then an *increase* in the digoxin dose would be more appropriate to compensate for the loss of inotropic effect due to quinidine, despite the further increase in serum digoxin concentration that would accrue. The third alternative is that some of the toxic effects of digoxin are extracardiac in origin (for example, central nervous system-related), whereas other toxic effects are of the same mechanism as the inotropic effects. This alternative would create a therapeutic dilemma. To clarify these issues, further research in a double blind prospective fashion is needed to determine if the increase in serum digoxin concentration resulting from the digoxin-quinidine interaction is associated with an increased or decreased risk of digitalis toxicity.

Acknowledgment

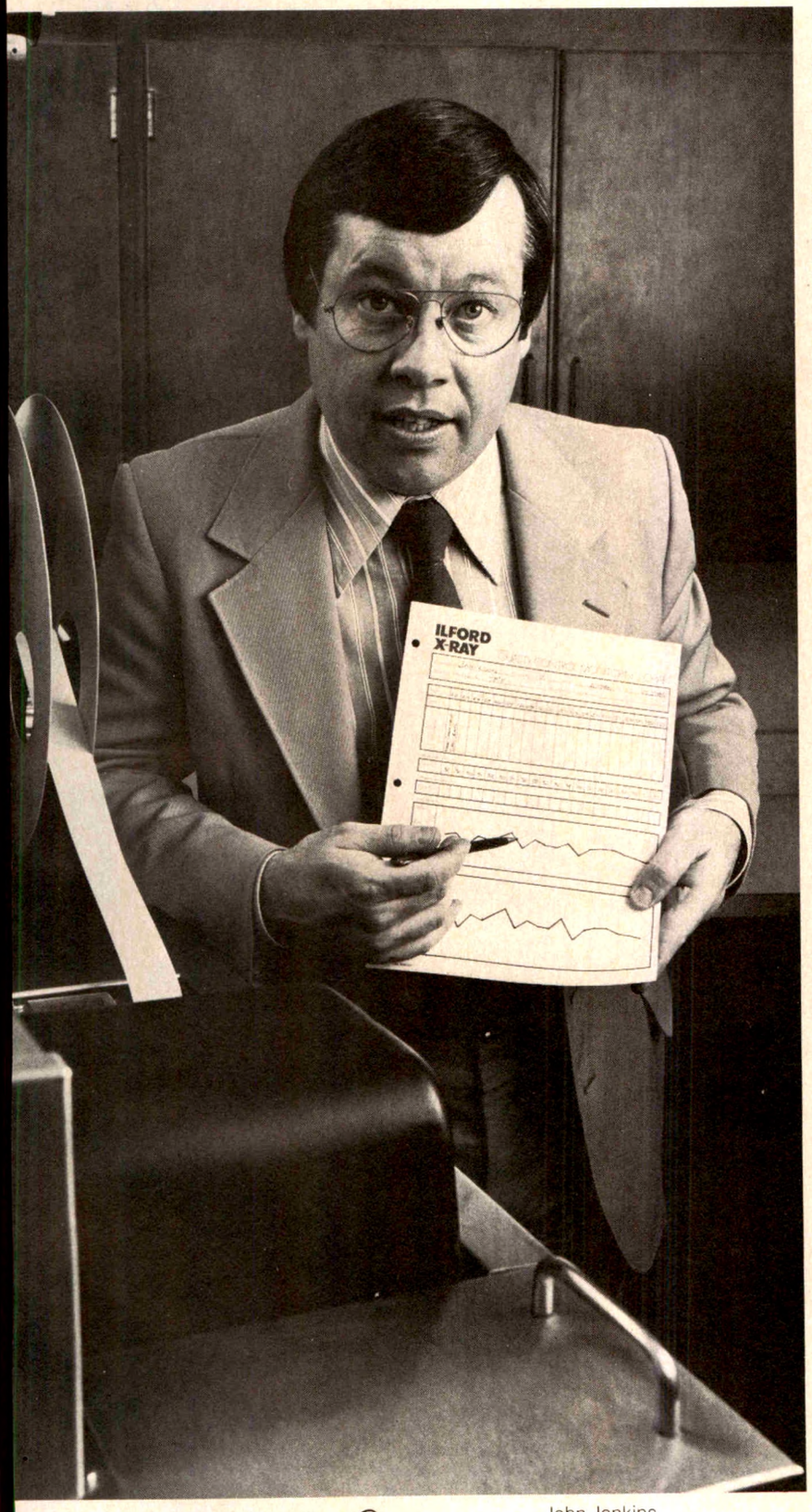
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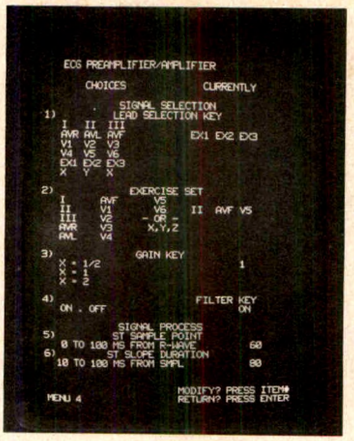
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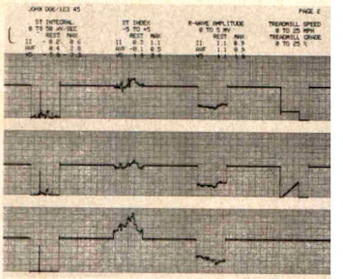
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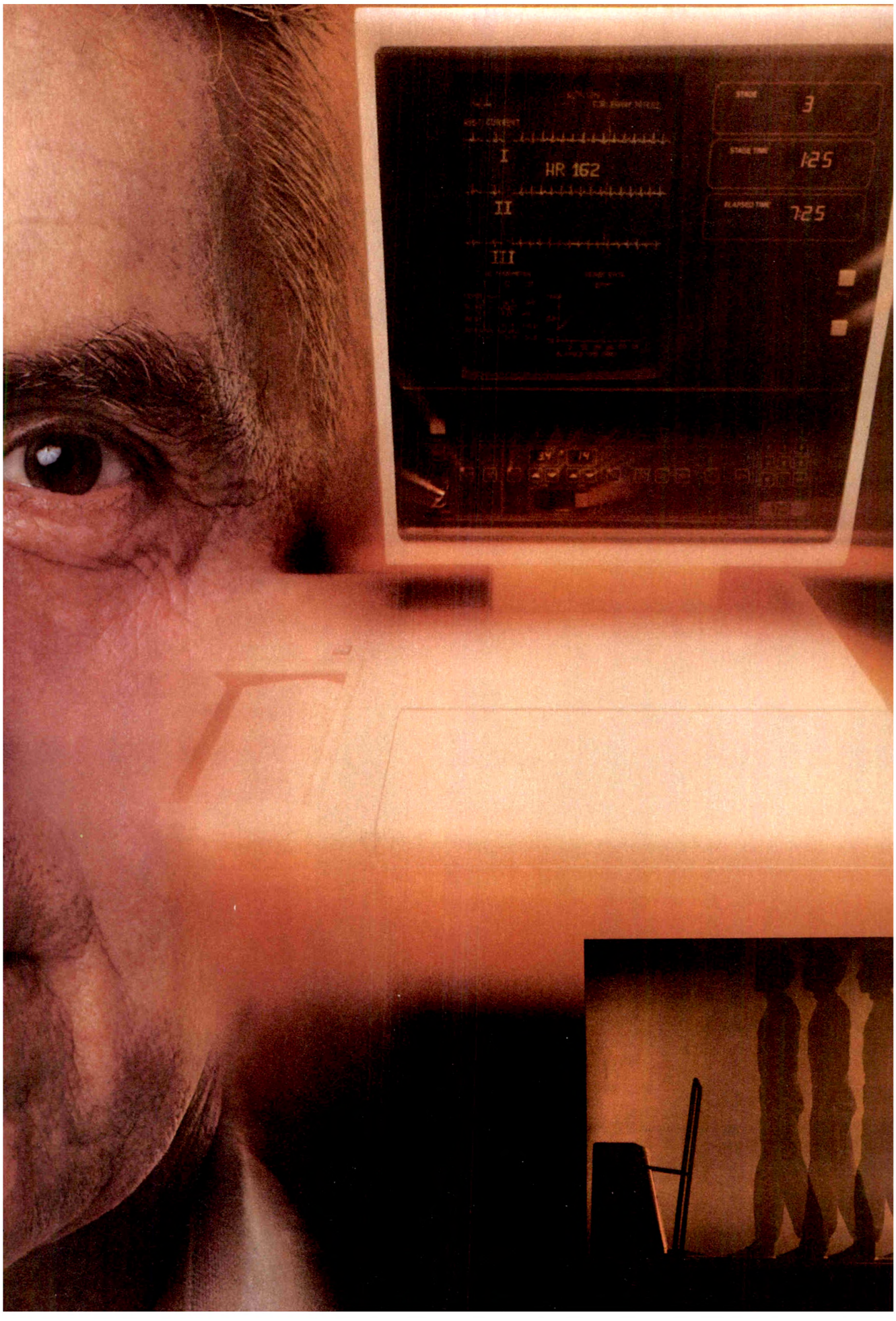
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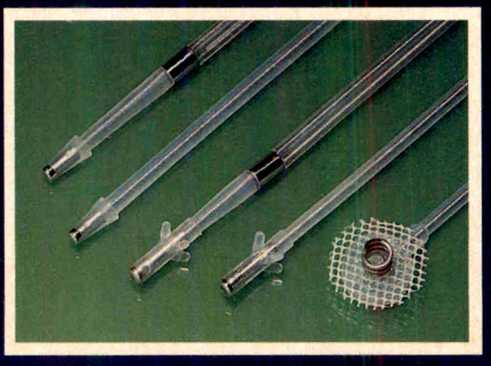

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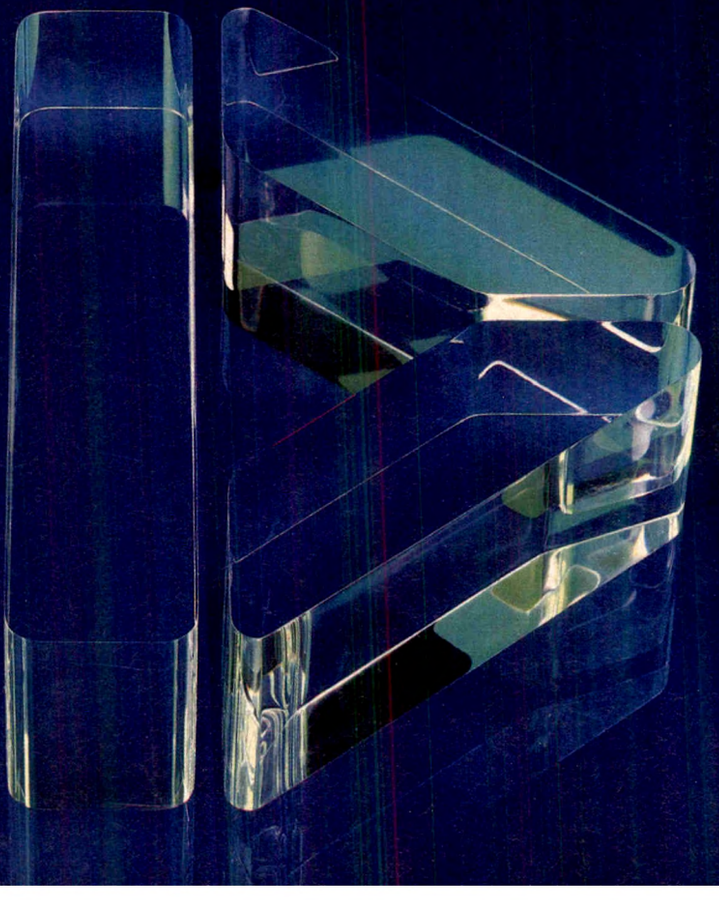
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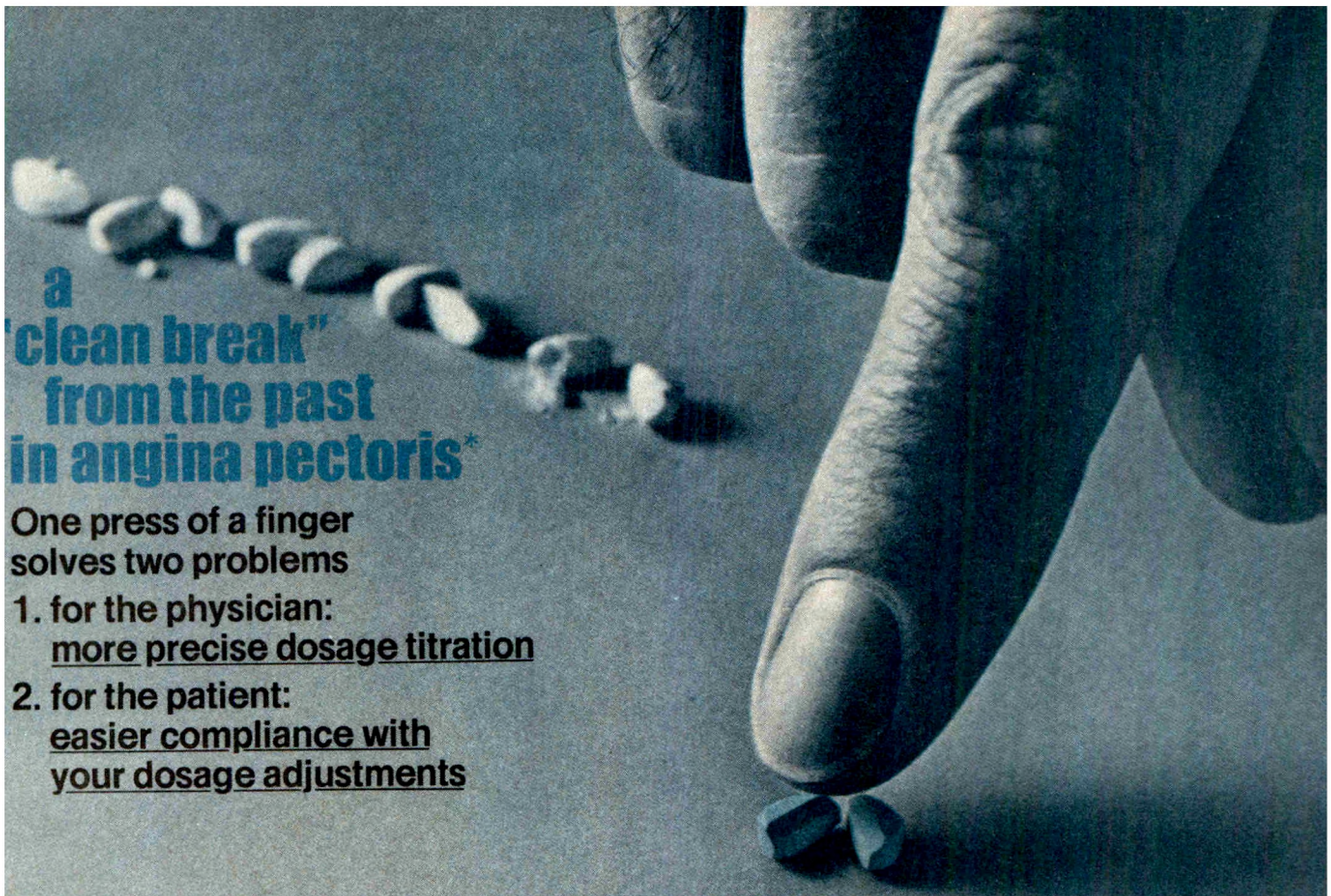


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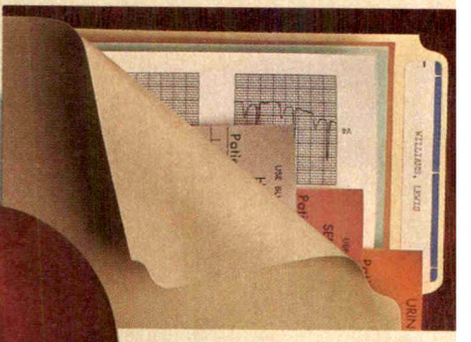
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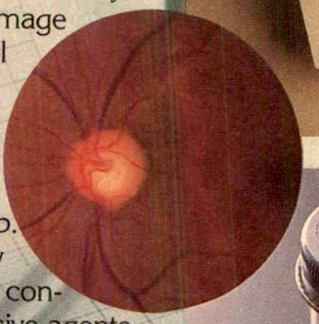
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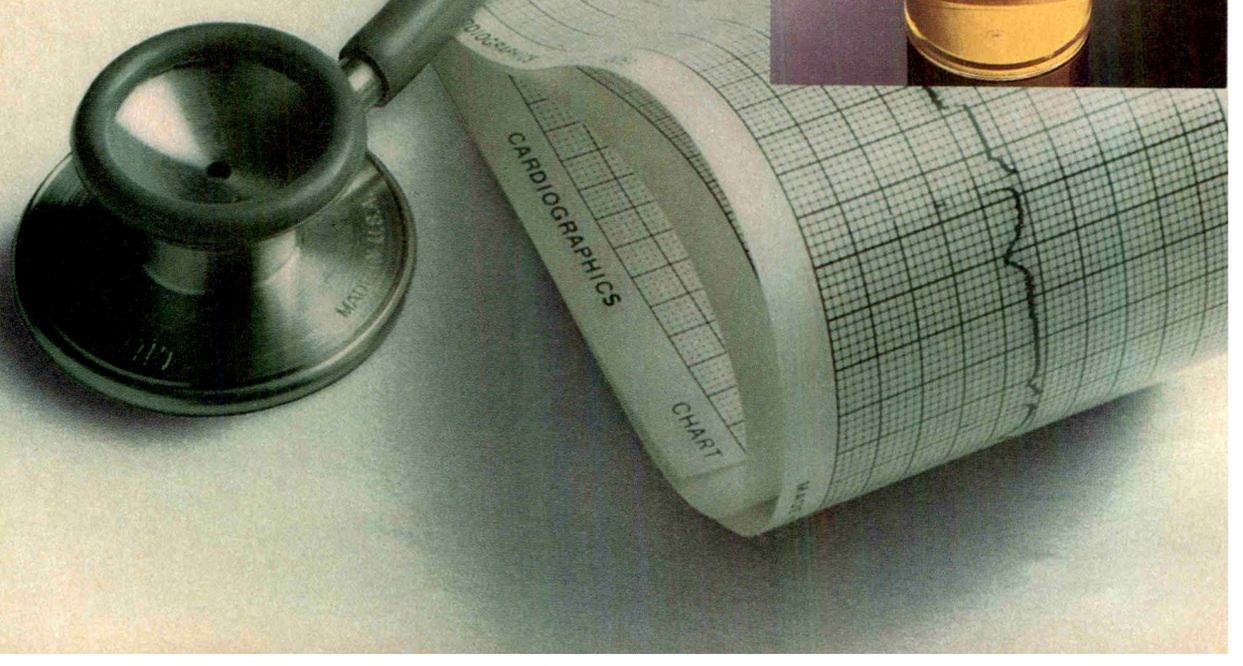
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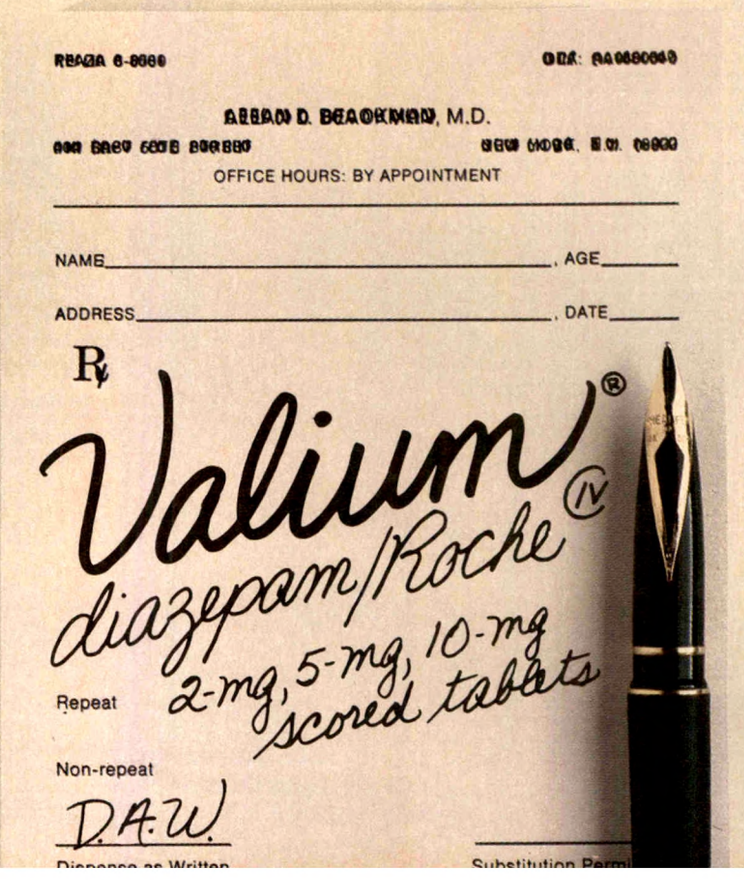


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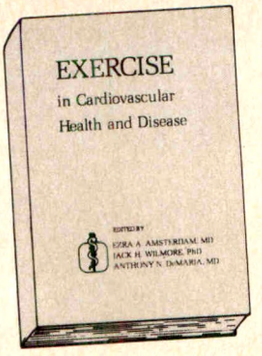
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Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

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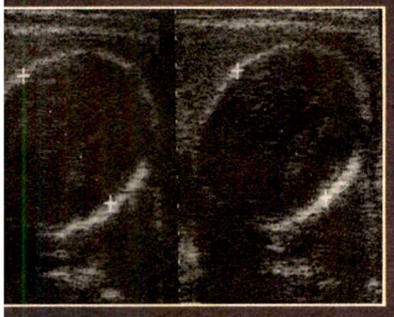
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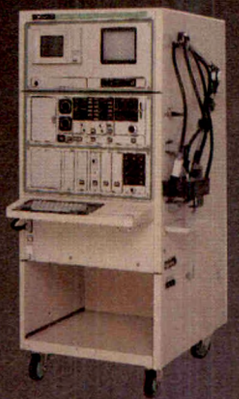
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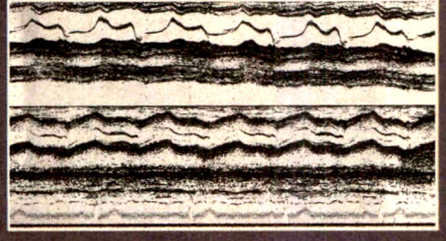


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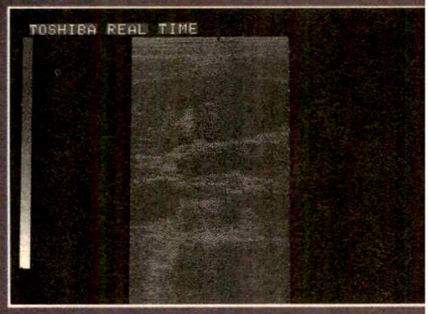


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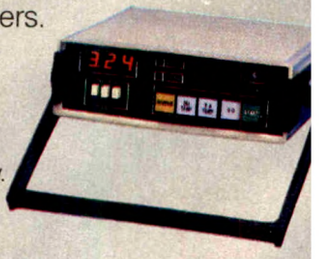
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Differentiation of Left Ventricular Pseudoaneurysm From True Aneurysm With Two Dimensional Echocardiography

ROBERT P. GATEWOOD, Jr., MD
NAVIN C. NANDA, MD, FACC

Rochester, New York

Real time two dimensional echocardiographic findings in four patients with a pathologically proved left ventricular pseudoaneurysm were compared with those in seven patients with a similarly proved true aneurysm of the left ventricle. Pseudoaneurysms produced a bounded echo-free space with a narrow neck that communicated with the left ventricular cavity. The maximal internal width of this neck (O_{max}) was much smaller than the maximal parallel internal diameter (D_{max}) of the aneurysmal sac, and the ratio O_{max}/D_{max} never exceeded 0.5. In all cases the pseudoaneurysm could be seen extending behind the intact portion of the involved left ventricular wall, and this finding produced a characteristic beak-like configuration in the studies of two patients. In contrast, true aneurysm resulted in local bulging and dilatation of the left ventricular wall so that the maximal internal width of the mouth (O_{max}) was nearly equal to, or actually represented, the maximal internal diameter (D_{max}) of the aneurysm so that the ratio O_{max}/D_{max} ranged from 0.9 to 1.0. Our preliminary study indicates that real time two dimensional echocardiography is useful in differentiating pseudoaneurysm from true aneurysm of the left ventricle.

Unlike true aneurysms, pseudoaneurysms of the left ventricle commonly rupture, leading to sudden death.[1,2] This complication can be successfully prevented by surgical repair.[3,4] Therefore, early recognition of a left ventricular pseudoaneurysm and differentiation from a true aneurysm is important. Unfortunately, because the clinical presentation of true and false aneurysm are similar, distinguishing between them has previously required cardiac catheterization and contrast cineangiography.[1,4,5] Although the potential diagnostic usefulness of real time two dimensional echocardiography has been reported in patients with true[6,7] and false[8–10] aneurysm of the left ventricle, there is a need for a comparative study using this technique to differentiate such patients. In this study we describe the two dimensional echocardiographic findings in four patients with pathologically confirmed pseudoaneurysm[11,12] and compare these findings with those in seven patients with a similarly proved true aneurysm of the left ventricle.

Methods

Patients: The 11 patients studied represented all adult patients with left ventricular aneurysm seen in our institution over a period of 18 months who had adequate two dimensional and M mode echocardiographic studies as well as pathologic confirmation of the nature of their aneurysm. The patients were separated into two groups on the basis of the pathologic nature of their aneurysms. Group I (Cases 1 to 4) consisted of patients with a pseudoaneurysm and Group II (Cases 5 to 11) of patients with a true aneurysm of the left ventricle (Table I). The pathologic criteria used for the diagnosis of a pseudoaneurysm were, on gross examination, the presence of a relatively small opening in the left ventricular wall providing a communication between the left ventricle and a large aneurysmal sac (Fig. 1A) and, on microscopic study, the absence of myocardial cells and coronary arteries within the fibrous walls of the aneurysm.[2,13] In con-

From the Cardiology Unit, Department of Medicine and the Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, New York. This study was supported by Research Training Grant HL 07220 in Cardiology from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received February 12, 1980; revised manuscript received June 16, 1980, accepted June 23, 1980.

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trast, the pathologic diagnosis of a true aneurysm was based on finding a wide-mouthed local bulging of the left ventricular wall (Fig. 1B) as well as the gradual transition from relatively normal myocardium to the thinner fibrous wall of the aneurysm, which retained some myocardial muscle cells and coronary arteries.[2,13]

Cardiac catheterization: Two patients (Cases 9 and 11) were critically ill when they first presented to the hospital and died before any invasive diagnostic procedure could be performed. The remaining nine patients underwent contrast left ventriculography and selective coronary cineangiography using the Judkins technique. Single plane left ventriculograms were taken in the right anterior oblique projection alone or with the left anterior oblique or lateral projection. The left ventriculogram was considered diagnostic of a pseudoaneurysm if an aneurysmal sac communicated with the left ventricular cavity by a narrow ostium.[14] In contrast, akinetic or dyskinetic wall motion accompanied by wall shape deformit resulting in a relatively wide-mouthed local bulging of th ventricular wall defined a true aneurysm of the left ventricle. Selective coronary angiograms from multiple views were als obtained.

Echocardiographic studies: Real time two dimensiona echocardiograms were performed in all patients using eithe a commercially available Picker (45 to 60°) or Advance Technology Laboratory Mark III wide angle (90°) mechanica sector scanner and recorded on a Sanyo videotape cassett The studies were performed using the standard transduce positions with the patient supine and in the left lateral de cubitus position.[16–18] In some patients tilting or pivoting c the transducer, or both, was necessary to effect oblique view through the left ventricle in order to visualize optimally th extent of the aneurysm and its mouth or neck. Sweeps acros multiple plane orientations with variations in gain and rejec

TABLE I

Clinical, Laboratory and Cardiac Catheterization Findings

Case	Age (yr) & Sex	Symptoms	Cardiac Findings	Electrocardiogram	Chest X-Ray Film	Cardiac Catheterization
			Group I (pseudoaneurysm)			
1	77F	Angina	PMI laterally displaced; palpable S_4; gr II/VI SEM; ? pleuropericardial rub	Old ASMI; VPCs	Cardiomegaly	Apical LV pseudoaneurysm; 100% occluded LAD
2	51F	CHF	PMI laterally displaced; palpable S_4; left parasternal impulse epigastric pulsation; gr I/VI early SEM	Small Q waves (<0.04 s); S-T↑ in leads II, III, aVF; VPCs	Cardiomegaly	Posterior LV pseudoaneurysm; grade 2/4 mitral regurgitation; 100% occluded RCA
3	38M	Angina	PMI laterally displaced; S_4	Old DMI with persistent S-T↑ and T↓; old ASMI	Cardiomegaly	Apical LV true aneurysm; severe 3-vessel CAD
4	64M	Embolic CVA	PMI laterally displaced; S_3 and S_4	Old DMI with persistent S-T↑; frequent VPCs	Cardiomegaly	Posterior LV aneurysm (true vs. false?); 100% occluded RCA; 85% occluded LAD
			Group II (true aneurysm)			
5	52F	CHF	PMI laterally displaced; S_3 and S_4	Old DMI with persistent S-T↑ and T↓; VPCs with intermittent VT	Cardiomegaly	Posterior LV true aneurysm; 100% occluded RCA; 75% occluded 1st marginal
6	52M	CHF; chest pain	PMI laterally displaced; MPP	Old DMI; old AMI with persistent slight S-T↑	Cardiomegaly	Anteroapical LV true aneurysm; 80 to 90% occluded LAD
7	57M	CHF; embolic CVA	PMI MCL 4th ICS; MPP; S_3; gr II/VI SEM	Old ALMI with persistent S-T↑	Local bulging along the left cardiac border c/w LV aneurysm	Anterolateral LV true aneurysm; 100% occluded LAD
8	54M	CHF; angina	PMI laterally displaced	Old ALMI with persistent S-T↑	Cardiomegaly	Anteroapical LV true aneurysm; 100% occluded LAD
9	69M	CHF	PMI laterally displaced; MPP; S_3; ? pleuropericardial rub	Old DMI; acute AMI; VPCs with intermittent VT	Cardiomegaly	. . .
10	29M	CHF	PMI laterally displaced; MPP	Old ALMI with persistent S-T↑	Cardiomegaly with cardiac contour c/w LV aneurysm	Apicoanterolateral true aneurysm; 100% occluded AD
11	61M	CHF	PMI laterally displaced; S_3 and S_4; gr II/VI holosystolic murmur	Old ALMI with persistent S-T↑	Cardiomegaly	. . .

ASMI = anteroseptal myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; c/w = compatible with; DMI = diaphragmatic (inferior) myocardial infarction; gr = grade; ICS = intercostal space; LAD = left anterior descending; LV = left ventricular; MCL = mid clavicular line; MPP = medial paradoxical pulsation; PMI = point of maximal impulse; RCA = right coronary artery; SEM = systolic ejection murmur; S-T↑ = S-T segment elevation; T↓ = T wave inversion; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

were done routinely to verify the anatomic relations and to ensure their constancy. The echocardiograms were, therefore, obtained utilizing multiple planes and analyzed for the site and maximal internal width of the mouth or neck of the aneuerysm, which was designated O_{max} (Fig. 1). The measurement of O_{max} was obtained using the frame that demonstrated the greatest diameter of the neck or mouth of the aneurysm irrespective of its timing in the cardiac cycle. The maximal parallel internal diameter of the aneurysm, termed D_{max}, was then measured using the same frame in which O_{max} was found. In addition, the echocardiographic studies were examined for the presence or absence of paradoxical systolic expansion and echogenic material within the aneurysm consistent with clot.[19,20]

The echocardiographic features were then correlated with the surgical and pathologic findings. In three patients with left ventricular pseudoaneurysm the two dimensional echocardiograms were performed before cardiac catheterization and provided a prospective diagnosis. In the fourth patient with a left ventricular pseudoaneurysm (Case 2) the echocardiogram was obtained after diagnostic contrast left ventriculography. In the seven patients with true aneurysm the echocardiographic diagnosis was made before cardiac catheterization in all five who underwent catheterization and before death in the two patients (Cases 9 and 11) whose condition was too unstable to permit any invasive procedure. Therefore, the two dimensional echocardiographic studies provided a prospective diagnosis in 10 of the 11 patients.

M mode studies were also performed in all patients in the standard manner[21] using Picker or Advanced Technology Laboratory equipment. Both the M mode and two dimensional studies were analyzed by two independent observers.

Results

Clinical findings (Table I): The average age in the patients in both groups was similar (57.5 years in Group I with pseudoaneurysm and 53.4 years in Group II with true aneurysm). Patients in both groups presented with congestive heart failure, chest pain, thromboembolic phenomena or ventricular arrhythmia, or combinations of these. On physical examination, an abnormal precordial movement suggesting the presence of a left ventricular aneurysm was recognized in four of the seven patients with true aneurysm (Cases 6, 7, 9 and 10). In the group with pseudoaneurysm, one of the four patients (Case 2) had a left parasternal impulse and prominent epigastric pulsation that in retrospect was thought to be secondary to the pseudoaneurysm and that could not be appreciated after surgical repair. Electrocardiographically, three of the four patients with pseudoaneurysm and six of the seven patients with true aneurysm had persistent S-T segment elevation. Ten of the 11 patients had electrocardiographic evidence of an old myocardial infarction (Q waves of 0.04 second or greater). Routine chest roentgenograms were diagnostically insensitive and demonstrated a local bulging in the left ventricular silhouette compatible with an aneurysm in only 2 of the 11 patients (Cases 7 and 11).

Cardiac catheterization findings (Table I): Left ventriculography accurately demonstrated the presence of a true aneurysm and localized its site of involvement in all five patients in Group II who underwent catheterization. In contrast, only two patients in Group I (Cases 1 and 2) were thought to have a left ventriculogram diagnostic of pseudoaneurysm. In the third patient (Case 4) marked cardiomegaly in conjunction with a huge posterior wall pseudoaneurysm led to very faint opacification of the aneurysmal sac, which was only partially included in the cineangiographic field. Hence, no definite conclusion as to the type of aneurysm in this group could be reached based on the angiographic study. Despite contrast injections in both the right and left anterior oblique projections, the fourth patient (Case 3) was diagnosed as having a moderately sized left ventricular apical aneurysm, probably of the true variety because a narrow communication with the left ventricular cavity was not visualized. All nine patients were found to have significant coronary artery disease (greater than or equal to 75 percent obstruction of luminal diameter of one or more of the three major coronary arteries).

Echocardiographic findings in pseudoaneurysm (Table I): The most impressive feature in Group I was that in all cases the left ventricular cavity could be seen communicating with another bounded echo-free space through a relatively small opening (1.4 to 3.0 cm) in the left ventricular wall (Fig. 2 and 3). In every patient, the maximal internal width of this communication (O_{max}), which formed the neck or opening of the pseudoaneu-

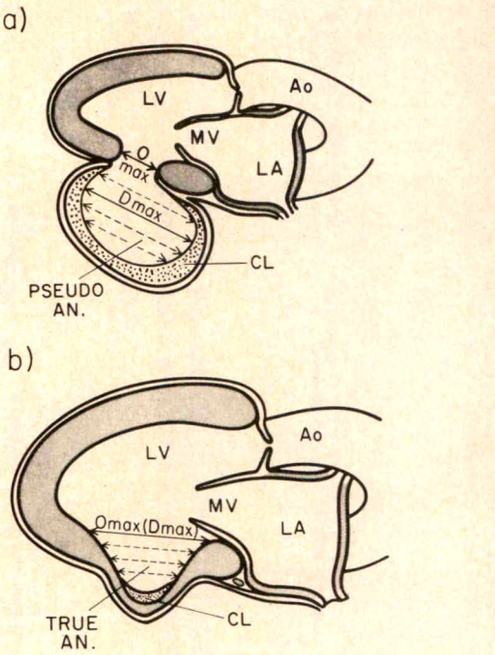


FIGURE 1. Schematic illustrations of the two types of left ventricular aneurysm. **a,** in a pseudoaneurysm (PSEUDO AN.) the maximal internal width of its neck or opening (O_{max}) is much smaller than the maximal parallel internal diameter (D_{max}) of the aneurysmal sac. **b,** in a true aneurysm (TRUE AN.) the maximal internal width of the mouth or opening (O_{max}) is usually equal to, or wider than, any other parallel internal diameter (←- - -→) of the aneurysmal cavity. Therefore, in this example O_{max} represents the maximal parallel internal diameter (D_{max}). Ao = aorta; CL = clot; LA = left atrium; LV = left ventricle; MV = mitral valve.

rysm, was much smaller than the maximal parallel internal diameter (D_{max}) of the aneurysmal sac (3.0 to 9.5 cm), resulting in an O_{max}/D_{max} ratio of 0.5 or less. This communication was located in the apical region in two patients and in the posterior wall proximal to the posterior papillary muscle in the other two. The aneurysmal sac could be seen to extend behind the intact portion of the involved wall of the left ventricle in all cases and in two produced a characteristic beak-like configuration (Fig. 2). The aneurysmal sac demonstrated paradoxical expansion during systole in three patients; no motion was apparent in one. In three patients the wall of the pseudoaneurysm appeared to be unduly thick, suggesting the presence of a thick clot that was subsequently found at surgery to be lining the wall (Fig. 2).

The diagnosis of left ventricular pseudoaneurysm and the site of the opening in the left ventricular wall as determined with echocardiography were confirmed in all cases at surgery or at autopsy. The echocardiographic measurements of O_{max} and D_{max} closely corresponded to those calculated at autopsy in Case 4 (3.0 and 9.5 cm versus 2.5 and 11.0 cm, respectively). In the remaining three patients exact measurements were not taken at surgery and, therefore, verification of the echocardiographically calculated diameters could not be obtained. In only one of the four patients was a localized echo-free space recorded with M mode echocardiography. This space was seen behind the posterior wall of the left ventricle but no communication with the left ventricular cavity could be identified, making it impossible to distinguish it from other causes of an echo-free space suc as a loculated posterior pericardial effusion.

Postoperative echocardiographic studies, availab in two (Cases 2 and 3) of the three patients who survive surgery, demonstrated disappearance of the previous described bounded echo-free spaces (Fig. 4).

Echocardiographic findings in true aneurys (Table II): In Group II the characteristic feature wa a localized out-pouching and dilatation of the involve wall that was present throughout the cardiac cycl Thus, the maximal internal width of the mouth (opening of the aneurysm (O_{max}) was relatively large, an in six of our seven cases represented the maximal pa allel internal diameter of the aneurysm (D_{max}) (Fig. 5 In contrast to the findings in pseudoaneurysm, th O_{max}/D_{max} ratio was always greater than 0.5 (range 0 to 1.0). The aneurysm was not observed to extend b hind the intact portion of the involved segment of th left ventricular wall in any of the seven patients with true aneurysm. Likewise, a beak-like configuration wa not found in any patient with a true aneurysm. Para doxical systolic expansion of the aneurysmal wall wa present in all seven patients. In addition, echogeni material lining the wall of the aneurysm was observe in all four patients found to have laminated clot withi the aneurysm at surgery or at autopsy.

Based on the surgical and autopsy findings, th echocardiographic studies accurately predicted the le ventricular wall involved in the formation of the aneu rysm in all seven patients (apical in three patients, ar

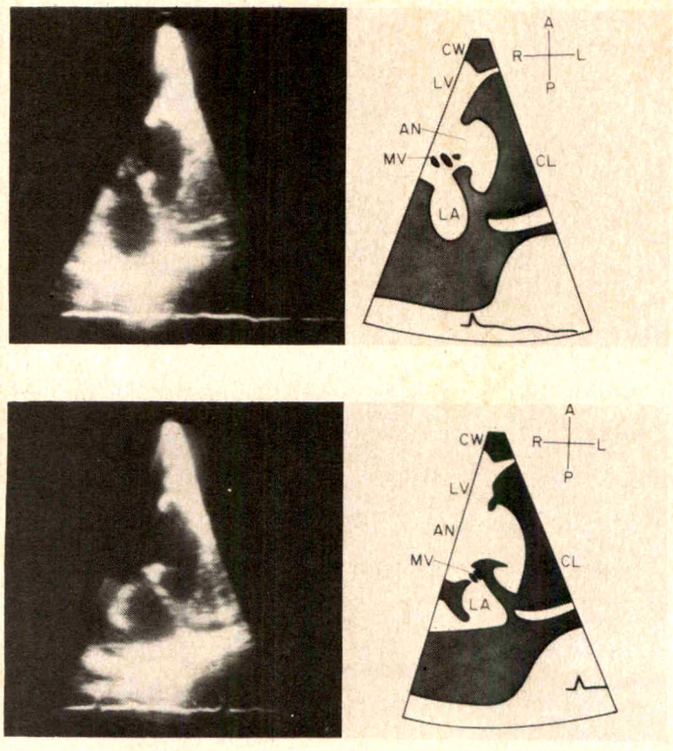
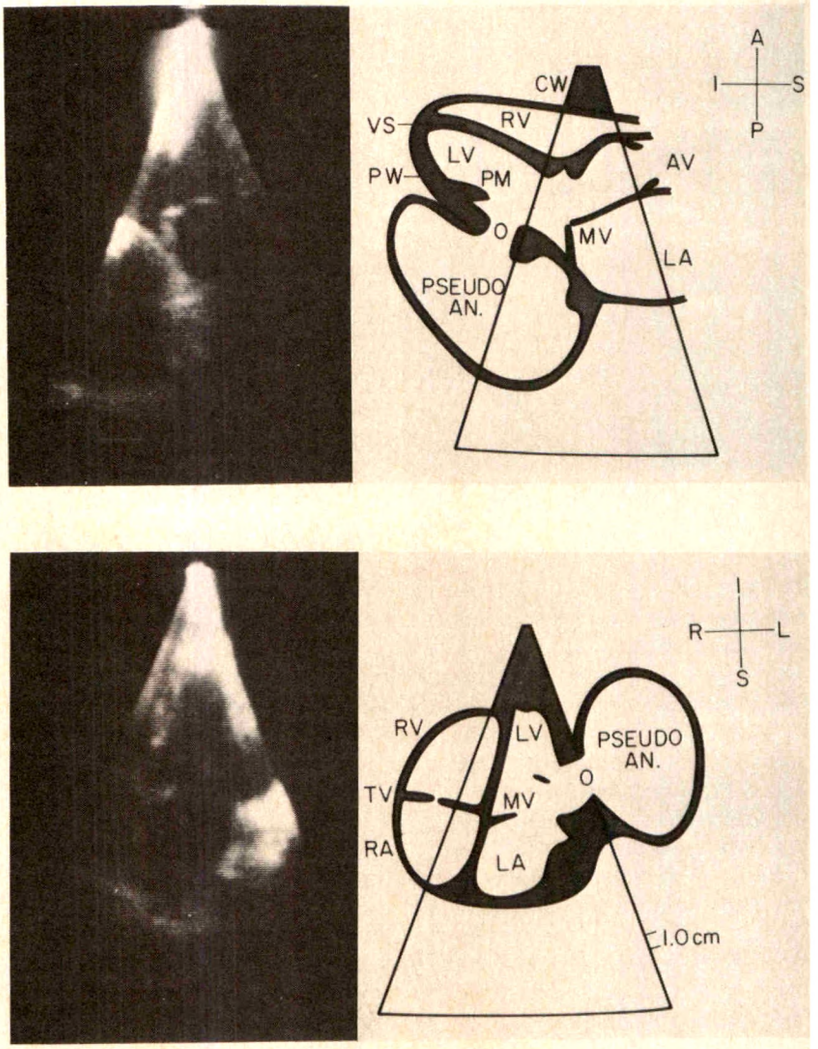


FIGURE 2. Case 2. Left ventricular pseudoaneurysm. With th transducer at the cardiac apex, the pseudoaneurysm (AN) present as a bounded echo-free space extending behind the intact segmer of the posterior wall of the left ventricle (LV), producing a charac teristic beak-like configuration. The maximal internal width of it neck or opening is half the maximal parallel internal diameter of th aneurysmal sac (2.5 and 5.0 cm, respectively). The walls of th aneurysm are unduly thick because of the presence of clot (CL Diastolic (**upper panel**) and systolic (**lower panel**) frames demor strate paradoxical systolic expansion of the aneurysmal sac. A = anterior; CW = chest wall; L = left; LA = left atrium; MV = mitra valve; P = posterior; R = right.



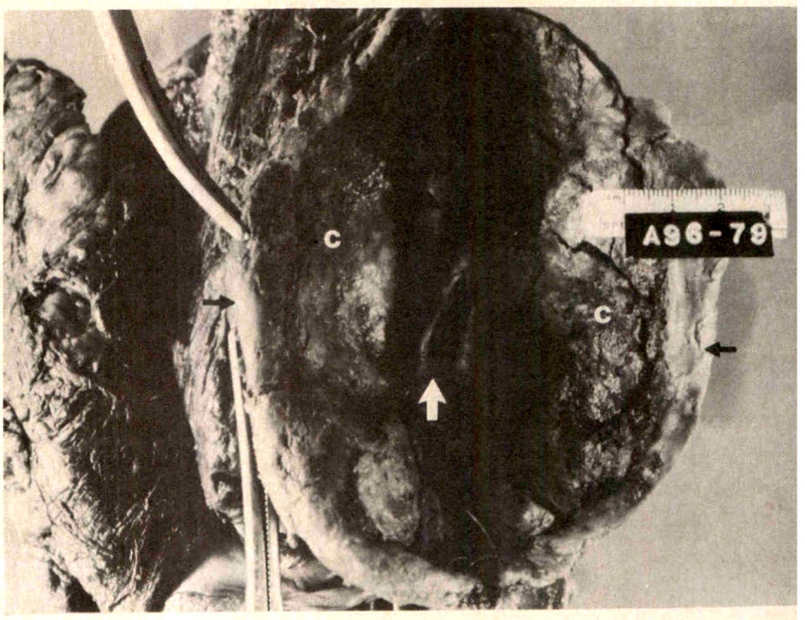


FIGURE 3. Case 4. Left ventricular pseudoaneurysm. **Upper panel,** the long axis view of the mitral valve demonstrates the pseudoaneurysm (PSEUDO AN.) as a bounded echo-free space behind the left ventricular posterior wall (PW) proximal to the posterior papillary muscle (PM). **Middle panel,** an apical four chamber view shows the neck or opening (O) of the pseudoaneurysm, which was much smaller than the maximal parallel internal diameter of the aneurysmal sac (3.0 and 9.5 cm, respectively). Sweeping the ultrasonic beam inferiorly and superiorly in the long axis plane and medially and laterally in the apical four-chamber plane confirmed the constancy of a "break" in the left ventricular posterior wall and its continuity with the bounded echo-free space. The echocardiographic diagnosis of a left ventricular pseudoaneurysm was made prospectively. **Lower panel,** the pathologic specimen shows the aneurysmal sac (**black arrows**) lined with clot (c) and the small opening (**white arrow**) in the left ventricular posterior wall. At autopsy the internal measurements of the neck and maximal parallel diameter of the aneurysmal sac (2.5 and 11.0 cm, respectively) correlated closely with the premorbid echocardiographic measurements. AV = aortic valve; I = inferior; RA = right atrium; RV = right ventricle; S = superior; TV = tricuspid valve; VS = ventricular septum. Other abbreviations as in Figures 1 and 2.

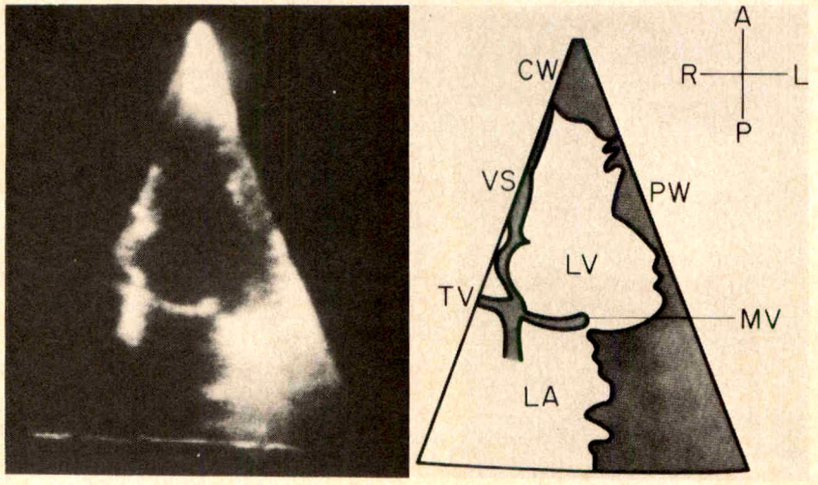


FIGURE 4. Case 2. Postoperative left ventricula pseudoaneurysm. The apical four chamber viev demonstrates structural continuity of the left ven tricular posterior wall (PW) throughout its entire lengtr There is no evidence of wall rupture with aneurysr formation that was present in the preoperative stud (Fig. 2). Abbreviations as in Figures 1 to 3.

terolateral in one patient, apical and anterolateral in two patients and posterior in one patient). Autopsy measurements of O_{max} and D_{max} were available in one patient (Case 9) and correlated closely with the premortem echocardiographic measurements (5.0 and 5.0 cm versus 5.7 and 5.7 cm, respectively). M mode studies failed to delineate convincingly the aneurysm in all seven patients. Postoperative two dimensional echocardiograms, available for review in two (Cases 7 and 10) of the four survivors, revealed no aneurysm.

Table II compares the real time two dimensional echocardiographic measurements found in true versus pseudoaneurysm of the left ventricle. There was no interobserver disagreement regarding the echocardiographic findings and measurements, which in both patient groups were analyzed by two independent observers.

Clinical course: All four patients in Group I (pseudoaneurysm) underwent surgical repair. Three (Cases 1 to 3) of the four patients survived surgery. All three of these patients are alive and well with partial o complete relief of symptoms.

Two patients with true aneurysm (Cases 9 and 11 died before surgery could be safely attempted. The re maining five patients in Group II underwent aneurys mectomy. One patient (Case 5) died 8 hours postoper atively, but the other four patients are alive and thei previous symptoms have been lessened.

Discussion

Left ventricular aneurysm is a common sequela and contributes to the morbidity and mortality in patients after myocardial infarction.[22] The majority of these aneurysms are of the true variety resulting from gradua fibrotic replacement of the infarcted myocardium.[2,13,2 In contrast a small proportion of these aneurysms are "false" or pseudoaneurysms that are formed as a consequence of rupture of the left ventricular wall with containment of the resulting hematoma by adherent

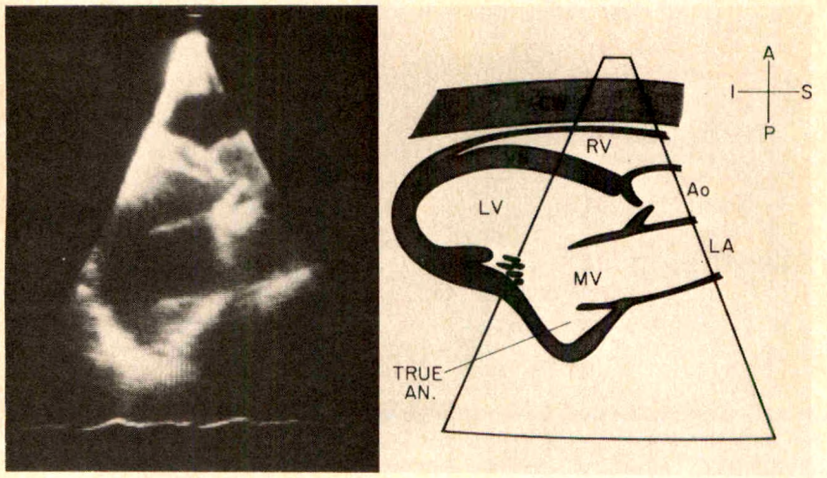


FIGURE 5. Case 5. Left ventricular true aneurysm. In the long axis view the true aneurysm (TRUE AN.) presents as a local outpouching and dilatation of the left ventricular posterior wall proximal to the posterior papillary muscle. The maximal internal width of the aneurysm represents the greatest diameter of the aneurysmal sac. Abbreviations as in Figures 1 to 3.

parietal pericardium or extracardiac structures, or both.[2,13,24]

Clinical and angiocardiographic diagnosis: Our experience underscores the conclusion of other investigators[1,10,13,24] that the clinical distinction between true and pseudoaneurysm of the left ventricle is difficult. In our patients no single or combined clinical or routine laboratory findings reliably identified pseudoaneurysm. Both types of aneurysm resulted in congestive heart failure, ventricular arrhythmias, persistent chest pain and thromboembolic phenomena. Cardiomegaly and persistent S-T segment elevation were common in both.

Although the premorbid diagnosis of left ventricular pseudoaneurysm has required cardiac catherization in the past, left ventricular angiography has some limitations as seen in two of our patients. If the X-ray beam is not oriented perpendicular to the neck of the aneurysmal sac, the aneurysm may overlap the left ventricle so that the left ventricular angiogram may only suggest a pseudoaneurysm or may actually simulate a true aneurysm (Case 3).[1,5,8,9] Restricting the amount of contrast material to be injected may result in incomplete opacification of a huge aneurysm, as in our Case 4, or limit the number of projections from which the aneurysm can be viewed.

M mode versus two dimensional echocardiography: Left ventricular aneurysms have not lent themselves to easy identification with noninvasive techniques such as M mode echocardiography. Pseudoaneurysms have been described to produce an echo-free space, generally behind the left ventricular posterior wall in the M mode scan.[8,10,25–28] Unfortunately, this finding is not specific because it is also seen in loculated posterior pericardial effusions. In addition, the M mode technique does not provide reliable visualization of the neck of the pseudoaneurysm. M mode findings of increased end-diastolic dimension with decreased wall motion at the apex compared with the base of the left ventricle,[29] localized displacement of the left ventricular wall,[30] abnormal motion of the anterior left ventricular wall[31] and convex systolic anterior motion of the mitral valve[32] may be suggestive but are not diagnostic of the presence of a true aneurysm. Real time two dimensional echocardiography has certain advantages over the M mode technique in distinguishing between true and pseudoaneurysm. Because it displays a wider segment of the heart, it can more accurately estimate the size of an aneurysm as well as visualize its anatomic relation to other surrounding structures and its communication with the left ventricular cavity. In all of our patients we were able to differentiate pseudoaneurysm from true aneurysm using the two dimensional technique. Pseudoaneurysms were characterized by a small neck whose maximal internal width never exceeded half the maximal parallel internal diameter of the aneurysmal sac, whereas true aneurysms had a wide mouth that was nearly equal to or actually represented the maximal parallel internal diameter of the aneurysm. Unlike true aneurysms, pseudoaneurysms extended behind the intact segment of the ventricular wall, thereby producing in some patients a characteristic beak-like configuration. Other features such as presence or absence of clot or paradoxical systolic expansion were not useful in the echocardiographic differentiation. In one patient with a pseudoaneurysm (Case 3) the diagnosis was not established with contrast left ventriculography, thus illustrating the potential advantage of two dimensional echocardiography in complementing the invasive procedure.

TABLE II

Two Dimensional Echocardiographic Measurements

Case	Location of Aneurysm	O_{max} (cm)	D_{max} (cm)	O_{max}/D_{max} Ratio
	Group I (pseudoaneurysm)			
1	Apical	1.4	5.5	0.25
2	Posterior	2.5	5.0	0.50
3	Apical	1.5	4.0	0.38
4	Posterior	3.0	9.5	0.32
	Group II (true aneurysm)			
5	Posterobasal	5.6	5.6	1.00
6	Apical	4.2	4.2	1.00
7	Anterolateral	6.0	6.0	1.00
8	Apical	5.1	5.1	1.00
9	Apical	5.7	5.7	1.00
10	Apical and anterolateral	7.0	7.0	1.00
11	Apical and anterolateral	4.5	5.0	0.90

D_{max} = maximal parallel internal diameter; O_{max} = maximal internal diameter of opening.

Comparison with previous reports: Roelandt et al.[8] were the first to report the two dimensional echocardiographic diagnosis of a pseudoaneurysm. They described a large localized echo-free space behind the left ventricular posterior wall but failed to confirm its communication with the left ventricular cavity. However, two subsequent case reports of pseudoaneurysms[9,10] clearly demonstrated a large bounded echo-free space connected to the left ventricular chamber by a relatively narrow ostium. The only full-length report addressing itself primarily to the two dimensional evaluation of left ventricular true aneurysm is that of Weyman et al.[6] All patients in their study had distinct localized aneurysmal bulging of the left ventricle, and all but one of their illustrations demonstrated a wide neck similar to our findings. Their Figure 8 shows a narrow neck leading to the aneurysm when the left ventricle was viewed in short axis using a narrow (30°) sector scanner, but no mention is made of the echocardiographic findings in other planes. In our series of patients the maximal width of the mouth or neck of the aneurysm was regularly found in standard or modified long axis or apical four chamber planes rather than in the short axis view, and it is conceivable that the atypical finding seen in this patient may be entirely explained by examination technique.

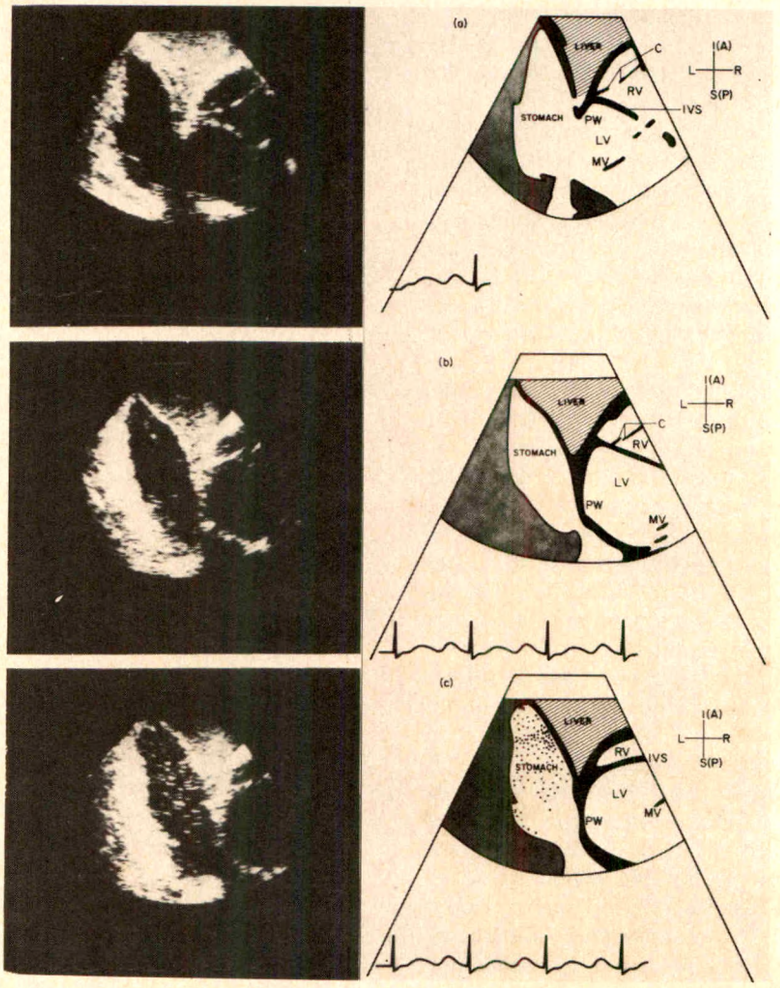


FIGURE 6. Simulation of pseudoaneurysm of left ventricle. **a,** in the subcostal view the stomach presents as a bounded echo-free space that appears to communicate with the left ventricle (LV) through the left ventricular posterior wall (PW), thus simulating a pseudoaneurysm. **b,** careful echocardiographic examination demonstrated inconstancy of this communication suggesting that it may be produced by echo "dropout." **c,** when the patient swallowed a bolus dose of water, a cloud of echoes appeared in the bounded echo-free space, confirming its gastric origin. These contrast echoes probably resulted from turbulence generated by the bolus streaming through the gastric air-fluid interface or by microbubbles of air present in the bolus itself. C = catheter; IVS = interventricular septum. Other abbreviations as in Figures 1 to 3.

Limitations of two dimensional echocardiography: Despite its diagnostic accuracy in our study, two dimensional echocardiography has several potential limitations. Because the orifice or neck of the pseudoaneurysm is of relatively small size, it may be missed. For this reason, the patient should be studied in various positions and with use of standard as well as oblique views. Even with proper technique, the communication may not be recognized if it is smaller than the width of the ultrasonic beam or if the pseudoaneurysm is inaccessible to the ultrasonic beam in a particular patient because of a small cardiac window or because of the size or anatomic location of aneurysm. Although never reported, it is possible that a pseudoaneurysm may be totally or nearly totally, filled with clot, thus obscuring the echocardiographic features of a pseudoaneurysm. However, if there appears to be a communication between a bounded echo-free space and the left ventricle, it is essential that it be distinguished from technical echo "dropout." This requires full examination using high and low gain and sweeps across multiple plane orientations ensuring constancy of the communication.

Differential diagnosis: Demonstration of a consistent communication between a large bounded echo-free space and the left ventricular cavity differentiates pseudoaneurysm from other entities, such as a loculated pericardiac effusion, pericardial cyst or other extracardiac cystic structures. A diverticulum of the left ventricle may produce a bounded echo-free space that communicates through a small channel with the left ventricular cavity,[33] thus producing echocardiographic findings identical to those found in pseudoaneurysms. However, pseudoaneurysm usually presents as a sequela

of myocardial infarction, as in all four of our patients, but occasionally occurs as a complication of surgery, trauma, endocarditis or an inflammatory process.[26] In contrast to pseudoaneurysm, left ventricular diverticuli are generally found in younger patients and may be associated with mid line thoracoabdominal defects.[34] In Figure 6 a bounded echo-free space produced by the patient's stomach appeared at times to communicate with the left ventricle (panel a) simulating a pseudoaneurysm in certain views. However, further analysis utilizing the aforementioned technique demonstrated inconstancy of the communication (Fig. 6b). In addition, a cloud of echoes appeared in this space when the patient swallowed a bolus dose of water demonstrating its gastric origin (Fig. 6c). Similar pericardiac echo-free spaces have been observed in five additional patients and confirmed to be related to the gastrointestinal tract by oral contrast studies.

With future developments in wider angle mechanical and phased array sector scanners and improvements in resolution, several of these potential limitations may be minimized. In fact, ventricular septal defects as small as 2 mm have recently been detected.[35]

Implications: Our preliminary experience suggests that real time two dimensional echocardiography may provide a safe noninvasive method for diagnosing pseudoaneurysm of the left ventricle and, therefore, may complement the clinical and angiographic evaluation in patients whose findings suggest this complication. Additional experience with a larger number of patients with left ventricular pseudoaneurysm is required to evaluate the sensitivity and specificity of this two dimensional echocardiographic method.

Acknowledgment

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Gallium-67 Citrate Scanning for Noninvasive Detection of Inflammation in Pericardial Diseases

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The treatment of acute nonspecific pericarditis is controversial. No study is available that confirms the efficacy of the administration of corticosteroids or nonsteroid anti-inflammatory agents in this condition. There is no reliable invasive marker for pericardial inflammation, because echocardigraphy demonstrates only the presence of fluid. In four patients with pericarditis, gallium-67 citrate scanning was performed, and the isotope was localized to the cardiac silhouette in all. In one patient with effusion the gallium scan was positive and then reverted to negative with corticosteroid therapy. In another, the gallium scan remained positive despite resolution of the pericardial effusion with corticosteroid therapy. This patient eventually required pericardial stripping. Pericardial localization of gallium was useful in detecting the cause of fever in a patient after aortocoronary bypass grafting and in detecting pericardial involvement in a patient with multisystem viral disease. Pericardial localization of gallium-67 may be diagnostically useful and may provide a proper control for the study of the efficacy of corticosteroids versus nonsteroid anti-inflammatory agents in pericarditis.

The therapy for acute nonspecific pericarditis not complicated by constriction or impending tamponade is controversial. Proponents can be found for corticosteroid, salicylate or indomethacin therapy. Corticosteroids have been the most frequently advocated agents, but no study has clearly demonstrated their long-term efficacy. Currently, the trend is toward the use of nonsteroid anti-inflammatory agents, presumably to circumvent steroid morbidity.[1] However, the enthusiasm and rationale for any type of pharmacologic intervention in this disease are not buttressed by proof of efficacy.

Echocardiography enables the clinician to monitor the course but not the character of a pericardial effusion. The development of a noninvasive reproducible technique for detecting, assessing and treating a pericardial inflammatory reaction is necessary before properly controlled clinical studies testing the efficacy of corticosteroids versus nonsteroid agents in nonbacterial pericardial inflammation can be completely interpreted.

Gallium-67 citrated scanning is an effective noninvasive method for detecting acute or chronic inflammatory reactions in the kidneys, bone, central nervous system and lungs.[2] Gallium-67 scanning in heart disease has been limited to detecting the site of valve involvement and myocardial abscesses in infective encocarditis,[3] to "hot spot" imaging in acute myocardial infarction[4] and to detecting myocardial inflammatory infiltrates in idiopathic congestive cardiomyopathy.[5] In this study we describe the results of gallium scanning in four patients with acute pericarditis in whom gallium-66 citrate localized to the cardiac silhouette.

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Methods

Patients: Gallium-67 citrate scans were performed in four patients with acute pericarditis. The diagnosis was based on the presence of one or more of the following: chest pain compatible with pericardial pain, pericardial friction rub or generalized S-T segment changes in the electrocardiogram and the absence of clinical or serum enzyme evidence of myocardial ischemia or infarction. Normal or stable left ventricular function based on multiple gated acquisition scanning, utilizing technetium-99m–labeled red blood cells, was also a prerequisite. In addition, 20 control patients underwent gallium-67 scanning, utilizing the special views of the chest, for reasons other than abnormal chest findings. This study was approved by the Loyola University Institutional Review Board for Protection of Human Subjects.

Gallium-67 scans: *The four patients* underwent imaging 72 hours after intravenous administration of 5 millicuries of carrier-free gallium-67 citrate. Images were performed in th anterior, the 45° and 60° left anterior oblique and the le lateral projections. The images were performed on a LFO gamma camera (Searle), using a 300 keV parallel hole coll mator. Triple pulse height analysis was routinely performec Twenty percent windows were centered about the 93 ke peak, the 184 keV peak and the 300 keV peak. Each projectio accumulated 500,000 full field counts. At the time of gamm camera imaging, the images were acquired into a fully prc grammable minicomputer in a 128 by 128 matrix. The effec tive grey scale of the images was altered by reducing the dis play range within the computer. In general, channels con taining 40 counts or less were not displayed. In no case was value in excess of 25 percent of the maximal channel valu used to delete low channel counts. Images were then photc graphed on either Polaroid® film or transparency film fc display. At the time of interpretation, images were graded o a scale of 0 to 4 as follows; grade 0, no definable activity withi

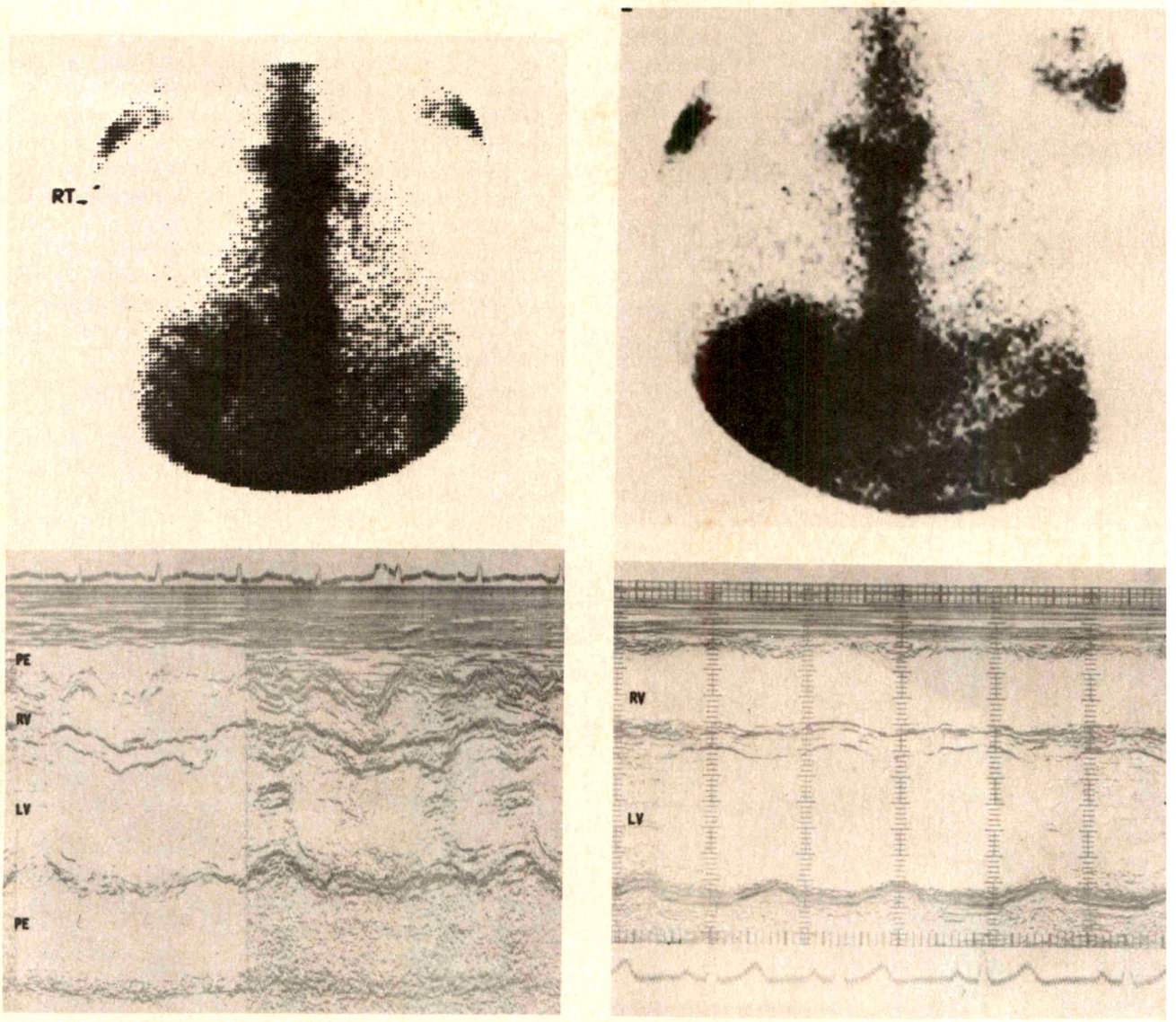


FIGURE 1. Case 1. **Top,** gallium-67 citrate scans of the anterior chest. In the initial scan (**left**), grade 2 diffuse uptake is evident. After 3 months of prednisone therapy (**right**), there is no abnormal gallium uptake. **Bottom,** M mode echocardiograms. The initial study (**left**) demonstrates the large echo-free spaces of pericardial effusion (PE). After prednisone therapy (**right**) the study demonstrates resolution of the effusion.

the chest structure; grade 1, barely perceptible activity over the myocardium; grade 2, definite myocardial visualization but less activity than that seen in the sternal area; grade 3, myocardial activity equal to that in the sternum; Grade 4, myocardial activity greater than that in the sternum.

In all 20 control patients, there was no significant uptake of gallium-67 citrate over the cardiac silhouette.

Results

Case Reports

Case 1: A 15 year old white boy had pharyngitis followed by pleuritic chest pain. The chest pain, which lasted 14 days, was worse in the supine position and was associated with mild fever and arthralgias. These symptoms were followed by fatigue, arthralgias and progressive anemia associated with a 4 kg weight loss.

On admission, 6 months after the onset of illness, the patient had low grade fever and a pericardial friction rub with no signs of tamponade or constriction. Active synovitis of the knees and small joints of the hands and wrists was noted. Laboratory data revealed a normochromic normocytic anemia, erythrocyte sedimentation rate of 70 mm in/hour, a positive rheumatoid factor in low titer of 1:40, and a positive antinuclear antibody with ribonucleoprotein specificities. Antistreptolysin titer was less than 100 Todd units. Cardiac enzymes were normal. The chest roentgenogram revealed marked increase in size of the cardiac silhouette and a small left pleural effusion. The electrocardiogram demonstrated sinus tachycardia and a P-R segment depression in leads II, III and aVF. An echocardiogram demonstrated a large pericardial effusion and normal left ventricular function. The presumptive diagnoses were rheumatoid arthritis and acute inflammatory pericarditis. A gallium-67 scan demonstrated grade 2 (when compared with sternal uptake) diffuse uptake over the myocardial region (Fig. 1, left).

Treatment with prednisone (1 mg/kg) and salicylates (2,400 mg/day) was initiated. Within 24 hours, fever and pleuritic chest pain had disappeared. All signs and symptoms of the pericardial effusion disappeared within 1 month, although the synovitis remained quite active. Administration of prednisone was tapered without exacerbating the pericarditis. Both the electrocardiogram and the echocardiogram were normal on follow-up study at 3 months. The chest roentgenogram revealed normal heart size and a minimal left pleural effusion. There was no pericardial uptake of gallium-67 citrate (Fig. 1, right).

Case 2: A 49 year old white woman presented to this center with a 3 month history of positional substernal chest pain that radiated to the left trapezius ridge. Initially, she had had an upper respiratory infection that required admission to a hospital, where an echocardiogram demonstrated pericardial effusion. The patient was successfully treated with corticosteroids, but the effusion recurred when therapy was discontinued at 6 weeks.

On this second admission, physical examination revealed a normotensive woman with no paradoxical pulse, but an audible and palpable pericardial friction rub. Routine laboratory findings were normal and antinuclear antibody test was negative. The chest roentgenogram demonstrated a normal heart size, and an electrocardiogram showed diffuse S-T segment depression. An echocardiogram confirmed the presence of posterior pericardial effusion. A gallium-67 scan of the chest, performed in the anterior projection, demonstrated a thin line of grade 2 gallium-67 uptake as a pericardial shadow (Fig. 2). A presumptive diagnosis of recurrent postviral pericarditis was made and prednisone therapy was instituted.

A second gallium scan was performed and was again positive as administration of prednisone was tapered. The echocardiogram revealed resolution of the pericardial effusion. Corticosteroid therapy was continued, but a pericardiectomy was performed in the 6th month of illness after early signs of constriction and persistent chest pain developed. At operation, the pericardium was noted to be thick with many fibrous adhesions. Histopathologic evaluation revealed fibrosis, fibrin deposits and chronic inflammation (Fig. 3). The patient recovered uneventfully and remains asymptomatic without corticosteroid therapy 6 months after operation.

Case 3: A 60 year old man was admitted for evaluation of postoperative fever 4 weeks after uncomplicated double aortocoronary bypass grafting. After operation, the pericardial friction rub disappeared by the 4th postoperative day and did not recur. The patient had chronic bronchitis and was taking prednisone (20

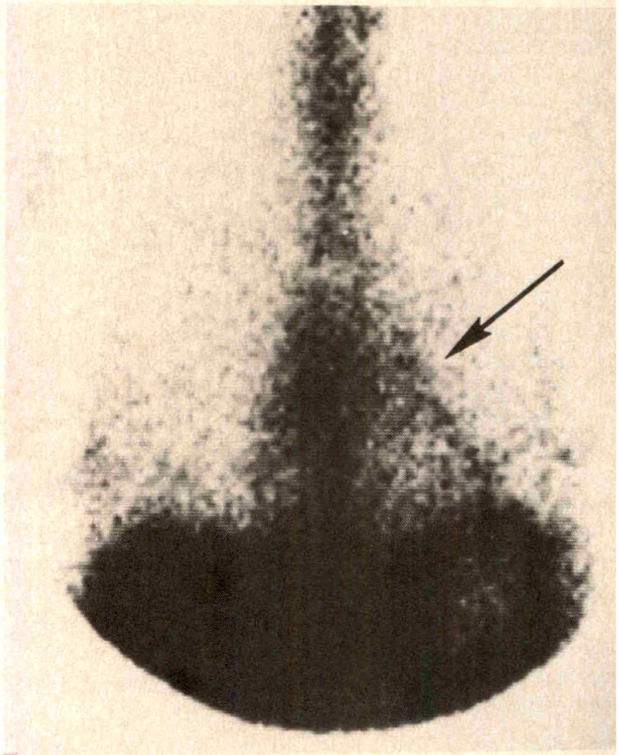


FIGURE 2. Case 2. Gallium-67 citrate chest scan, anterior view. **Arrow** indicates grade 2 isotope uptake localized to the pericardium.

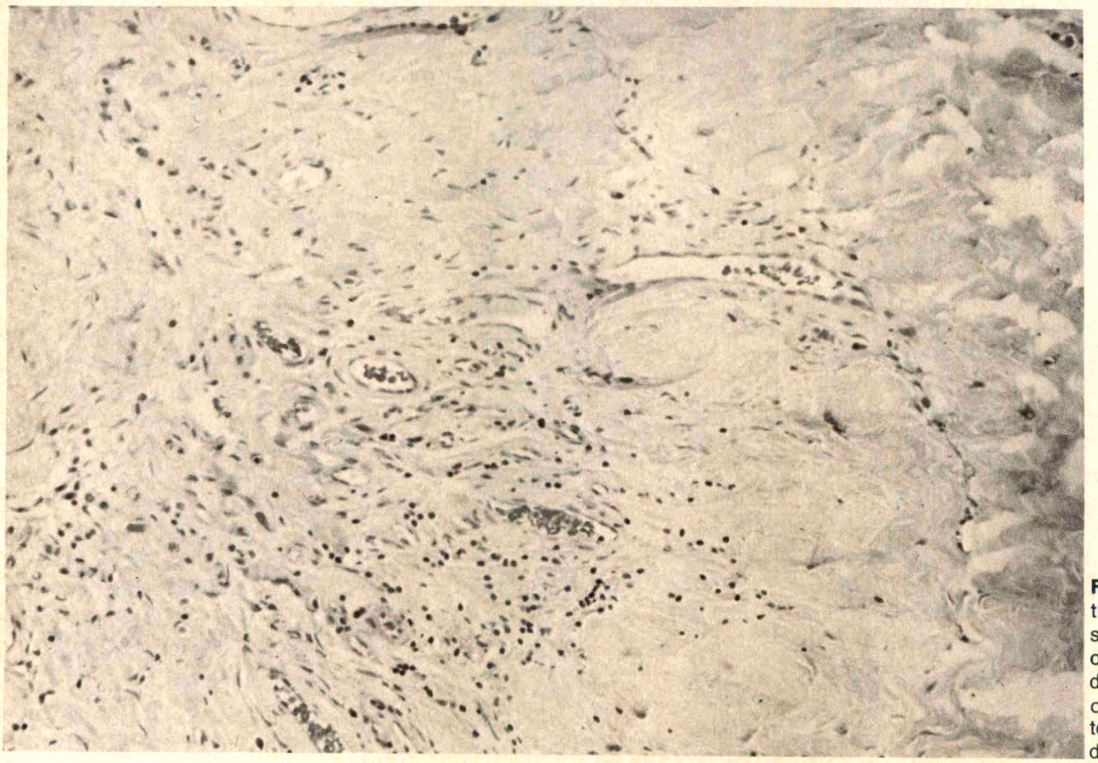


FIGURE 3. Case 2. Section from pericardial surgical specimen demonstrating fibrosis, fibrin deposition and mononuclear infiltration. (Hematoxylin-eosin ×125, reduced by 26 percent.)

mg/day) at the time of admission for aortocoronary bypass grafting.

Physical examination on this postoperative admission was normal. No pericardial friction rub was audible and there was no hepatomegaly. There was no evidence of acute ischemia or changing left ventricular function. Routine laboratory analysis revealed an erythrocyte sedimentation rate of 63 mm in 1 hour and a white blood cell count of 12,200/mm^3. A purified protein derivative test was positive, but sputum smear and cultures were negative for M. tuberculosis. Routine cultures were negative. The electrocardiogram showed nonspecific S-T wave changes. The chest roentgenogram was within normal limits. A gallium-67 scan of the chest demonstrated diffuse grade 2 uptake in the anterior mediastinum that was within the heart shadow in oblique projections.

The prednisone dose was increased to 60 mg/day after bacterial infection had been ruled out, and the patient's fever rapidly subsided. Because of the elevated sedimentation rate, the postoperative fever that defervesced immediately with steroid administration, and the nonspecific S-T wave electrocardiographic changes, a diagnosis of postpericardiotomy syndrome was made. The patient was maintained on prednisone therapy and his condition continued to improve. Two weeks after discharge, an echocardiogram was performed and was within normal limits. He is symptom-free at 2 year follow-up.

Case 4: A 71 year old white man was admitted with confusion, shortness of breath and weakness after a 2 week history suggestive of tuberculosis, purulent pericarditis or tumor. Pertinent findings included fever and supraventricular arrhythmia. Examination of the cerebrospinal fluid ruled out meningitis. The erythrocyte sedimentation rate was 108 mm in 1 hour. Antinuclear antibodies were absent, and a rheumatoid factor was present at a titer of 1:320. A purified protein derivative test was negative as were sputum cultures for M. tuberculosis. Routine cultures were negative. The chest roentgenogram demonstrated mild cardiomegaly and minimal pulmonary venous engorgement. The electrocardiogram showed atrial fibrillation with moderate ventricular response and generalized ST-T wave changes. Cardiac enzymes were normal on three occasions. An echocardiogram demonstrated a moderate anterior and posterior pericardial effusion and multiple gated acquisition scanning revealed normal wall motion with an ejection fraction of 55 percent in the left anterior oblique projection. A Swan-Ganz catheter was used for hemodynamic monitoring. Pressures (in mm Hg) were: mean right atrial, 4; right ventricular, 30/4; pulmonary arterial, 30/10; and pulmonary arterial wedge, 16. A gallium-67 scan was performed. The isotope localized diffusely with grade 4 density in the cardiac silhouette. The overall clinical picture suggested that this patient had multisystem viral disease, predominantly acute pericarditis and encephalitis.

Therapy with prednisone (60 mg/day) and azathioprine (200 mg/day) was begun on the 10th hospital day. Within 24 hours, the patient's condition improved dramatically and during the next 10 days, he became alert and oriented and started to walk; however, on the 20th hospital day he complained of the sudden onset of

substernal chest pressure, had no vital signs and could not be resuscitated. Permission for autopsy was denied.

Discussion

The treatment for acute nonspecific pericarditis complicated by tamponade is alleviation of acute hemodynamic compromise by surgical or percutaneous drainage. If the pericardial inflammation presents clinically with constrictive hemodynamics, surgical stripping is the accepted mode of therapy (both these therapeutic decisions are derived as pathophysiologic abnormalities with clinical end points of improvement). The treatment of acute nonspecific pericarditis uncomplicated by either tamponade or constriction is controversial. The symptoms of pain or arrhythmia may be alarming to the patient and deserve pharmacologic intervention even though these patients generally appear to have a more benign course than that of patients with tamponade.

Steroid versus nonsteroid therapy in pericardial inflammation: Treatment of nonspecific pericarditis with corticosteroids may result in dramatic relief of symptoms. Recurrent clinical symptoms may arise when this treatment is discontinued. Connolly and Burchell[6] described 27 patients with acute nonspecific pericarditis who were treated with corticosteroids. Initial improvement was noted in all, yet nine patients (33 percent) became corticosteroid-dependent. Of 101 patients with acute benign pericarditis followed up over an 18 year period, 80 percent of the patients who experienced a relapse had previously been treated with corticosteroids.[7] An overriding consideration with the use of corticosteroids is their long-term morbidity. Because clear-cut demonstration of their efficacy is still not available, several nonsteroid anti-inflammatory agents, especially salicylates and indomethacin, have been used.[1] To date, no study has demonstrated their efficacy. These nonsteroid agents may relieve the symptoms of postpericardiotomy syndrome, but the response is neither as complete nor as rapid as that seen with administration of corticosteroids.[8] The debate on the primary mode of therapy has been spirited, some investigators favoring nonsteroid antiinflammatory agents[1] and others recommending corticosteroids but exercising caution in their withdrawal.[9] Resolution of this important therapeutic decision may be aided by the development of a noninvasive reproducible marker that accurately detects pericardial inflammation. Once available, studies testing the efficacy of steroidal versus nonsteroid therapy for acute nonspecific pericarditis can be designed.

Echocardiography in pericardial inflammation: The development of echocardiography has provided the ability to monitor the course of a pericardial effusion. In some patients, chest wall configuration or chronic lung disease prevents adequate echocardiographic analysis. Loculation and adhesions may prevent effusions from being detected and false positive echoes may occur with prominent epicardial fat pads, pericardial cysts, foramen of Morgagni herniae, left pleural effusions, calcified mitral anuli and inordinately medial transducer angulation.[10] Many patients with acute nonspecific pericarditis never have effusion, precluding echocardiography as a useful tool in following their clinical course. A primary deficiency is the inability of echocardiography to differentiate characteristics of pericardial fluid. A transudative fluid will look similar to an inflammatory fluid with echocardiographic analysis and sequential assessment of anti-inflammatory drug efficacy is not possible.

Technetium-99m scintigraphy in pericardial inflammation: Thirty-two patients with acute pericarditis were studied with technetium-99m pyrophosphate scintigraphy within 4 days of onset of symptoms.[11] Only 11 (34 percent) had uptake over the cardiac silhouette. Another 20 patients with pericarditis were studied with technetium-99m pyrophosphate and uptake was noted only in patients with ischemic heart disease.[12] Theoretically, technetium-99m pyrophosphate should detect subepicardial necrosis that occurs during pericarditis but it appears to be relatively insensitive.

Gallium-67 citrate scintigraphy in pericarditis: The sensitive isotopic indicator of inflammation is gallium-67 citrate scintigraphy. Initially described as a bone scanning agent, gallium is recognized as an effective localizer of tumors and of either acute or chronic inflammatory lesions.[2] The vast majority of clinical information accumulated relates to gallium-67 detection of inflammation in the kidneys, bone, central nervous system and lungs. Application of this isotope to cardiac disease has just begun. Cardiac valves involved by infective endocarditis vegetations can be localized.[3] Gallium-67 has been used as a myocardial infarct-avid agent, but its low target to background ratios preclude its clinical utility.[2,4] We[5] previously investigated the utility of gallium-67 citrate in detecting active inflammation in patients with idiopathic congestive cardiomyopathy. It appears that gallium-67 citrate may have clinical potential in inflammatory processes involving the pericardium as well.

The four patients described demonstrate the ability of gallium-67 to detect pericardial inflammation. The uptake may be diffuse or localized.

In Patient 1, gallium-67 was useful in monitoring the response to the steroid therapy. Gallium-67 scanning in this instance correlated closely with the course of the pericardial effusion by echocardiogram. Although active small and medium joint synovitis persisted, we interpreted the development of a negative pericardial gallium scan after 3 months of therapy as supporting evidence for absence of inflammation, and corticosteroids were withdrawn without relapse.

Patient 2 illustrates the common clinical dilemma of recurrent symptoms despite echocardiographic resolution of the pericardial effusion as corticosteroids are withdrawn. Persistent cardiac gallium uptake stimulated clinical scrutiny for the early signs of constriction. Once it developed, surgery was successfully performed. Tissue obtained during the procedure had histologic evidence of inflammation.

In Patient 3, the diagnosis of postaortocoronary bypass graft fever was supported by localization of gallium-67 to the pericardium. The lack of demonstrable sources of infection and the rapid resolution of fever and lowering of the sedimentation rate in this patient indirectly confirm the diagnosis of postpericardiotomy syndrome. The criteria for diagnosis of the postpericardiotomy syndrome can be vague and clinically confusing. The gallium-67 localization may be of great value in this disease.

In Patient 4, gallium-67 scanning focused clinical attention to the pericardium in a patient with generalized multisystem disease. Corticosteroid therapy resulted in rapid resolution of symptoms.

All of these patients exhibited normal or stable myocardial function and no patient had electrocardiographic or serum enzyme evidence of acute myocardial infarction that would explain the gallium uptake ove the myocardium. The scans were performed at 72 hou to eliminate any question of blood pool imaging tha could account for the gallium concentration. All contr patients had negative gallium scans; moreover, nucle radiologists rarely note gallium uptake over the cardia silhouette in patients without heart disease.

Implications: The management of acute nonspecif pericarditis is not satisfactory. No controlled study ha been reported that incorporates a laboratory assessmer of inflammatory activity demonstrating superior eff cacy of corticosteroids or nonsteroid anti-inflammator agents. The observation that the inflammation-avi isotope, gallium-67 citrate, localized to the cardiac si houette in patients with acute pericarditis may provid the marker of inflammation that is necessary for thes studies to be successful.

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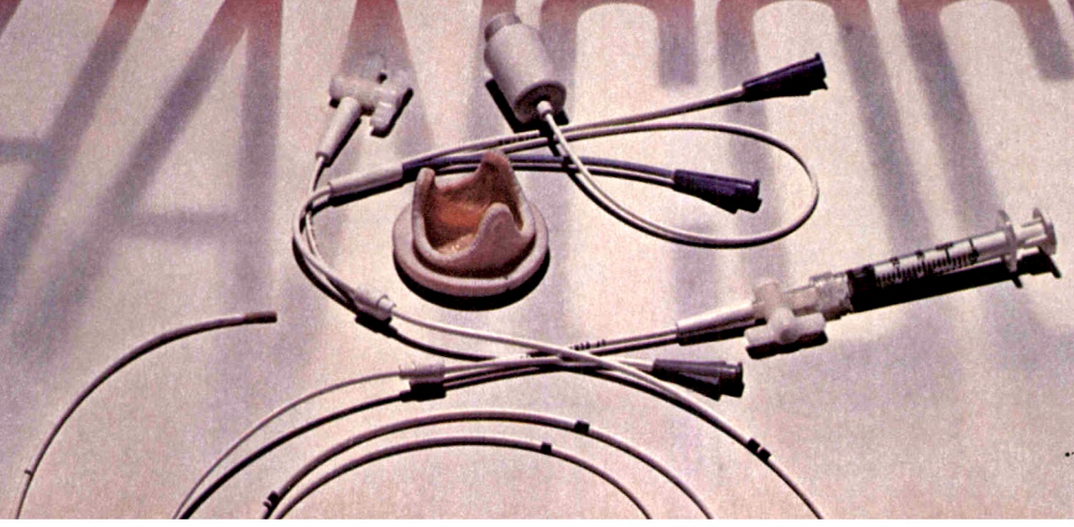
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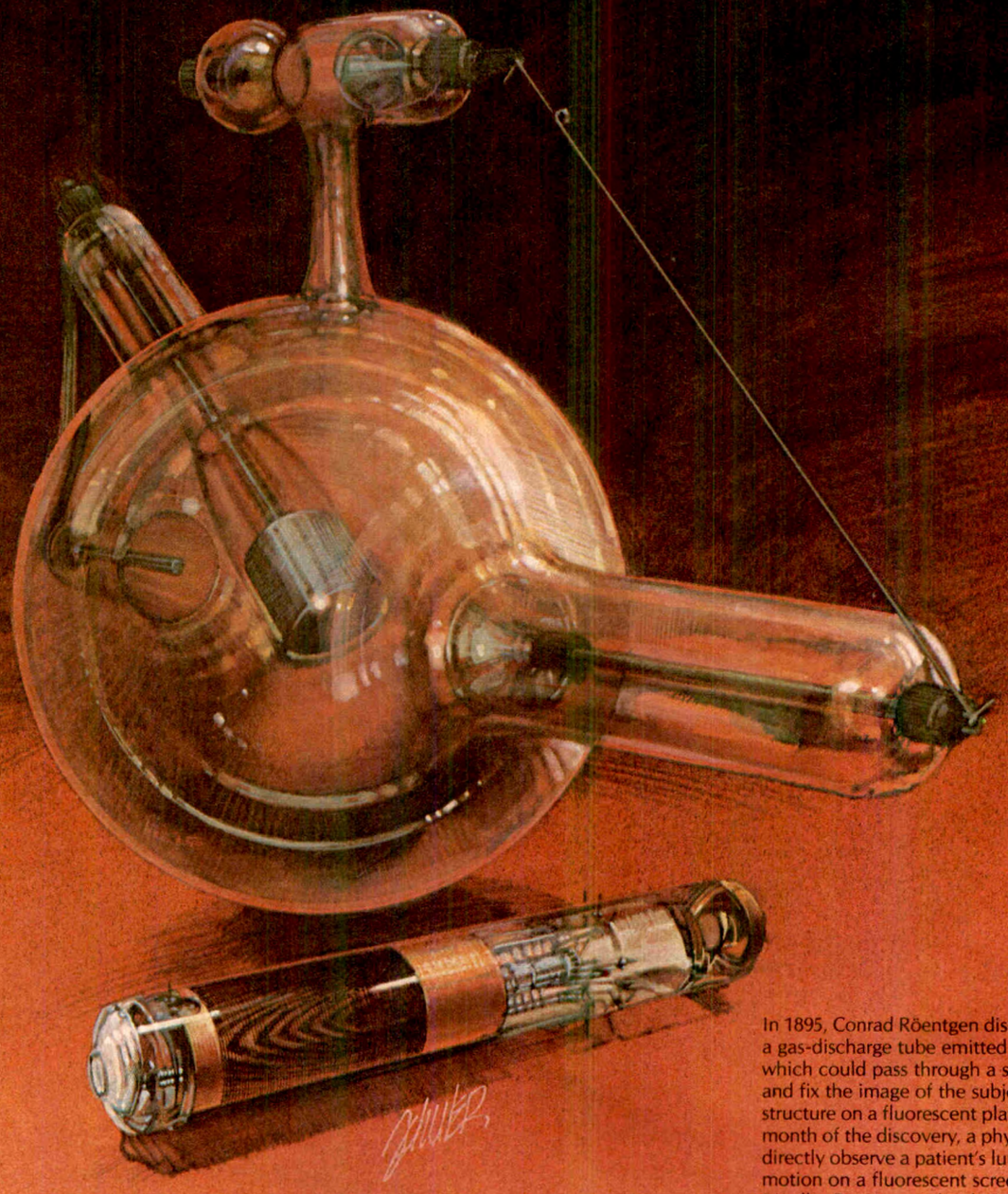
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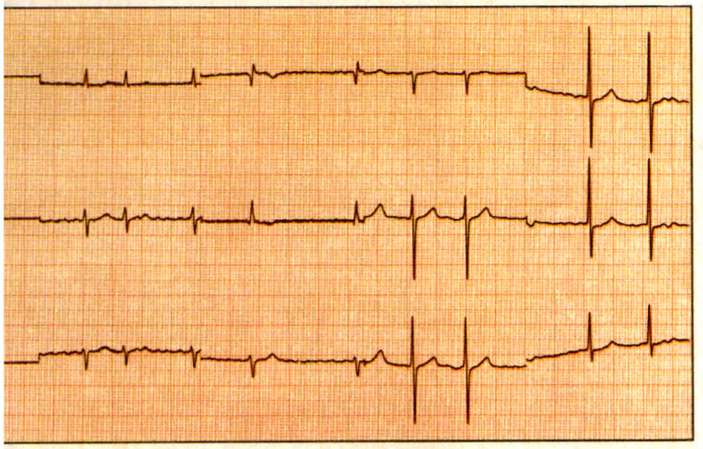
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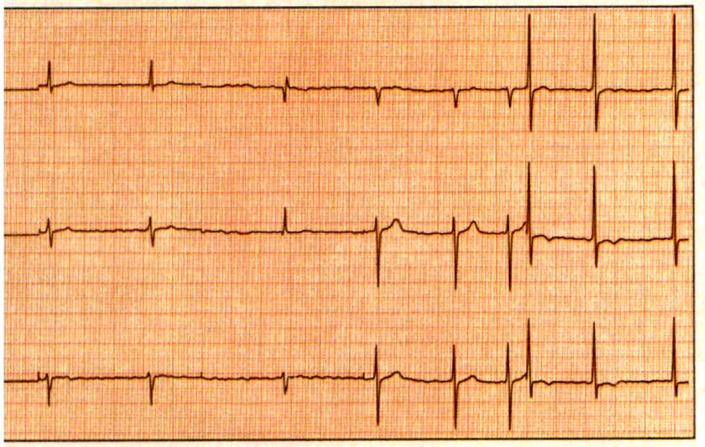
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omwell, L., et al: Biomedical Instrumentation and Measurements. Prentice-ll, 1973.

olf HK, Harris LK, Kanon DJ, and Prineas RJ: Identification of Myocardial arction by ECG, Interpreted by Computer and Cardiologist. Unpublished ta, Feb. 1980.

Comparison report suggests clinical implications of change.

TELEMED COMPUTER SERIAL COMPARISON (KO)

PATIENT ID: 332170000, DATE: 9-JAN-78 06:24:57 CENTRAL TIME
CODE: 498/79/2/0/0/2/0

INTERVALS: PR NOT MEASURED QRS (LIMB) = 0.098 QT = 0.41
AXES: P = °0 QRS = −47 T = 74
HISTORY: MALE−79 YEARS−MED. BLD−NO HX−RX UNKNOWN

INTERPRETATION:
CURRENT ECG: DATE: 1-9-78 TIME: 6:24:57
PREVIOUS ECG: DATE: 1-7-78 TIME: 10: 5:21

RHYTHM
ATRIAL FIBRILLATION PERSISTS
−MEDIAN RATE HAS INCREASED TO 67 (RANGE 39 TO 101)

FINDINGS
1) THERE IS PERSISTING EVIDENCE FOR LVH ON A NON-VOLTAGE BASIS.
2) QRS AXIS IS −47 DEGREES.
3) THERE ARE NO ST/T ABNORMALITIES (II, III, F) AND SINCE THE PREVIOUS TRACE T-WAVES ARE NO LONGER NEGATIVE IN THE INFERIOR LEADS. THERE ARE ST/T ABNORMALITIES IN THE LEFT PRECORDIAL/LATERAL LEADS AND SINCE THE PREVIOUS TRACE T-WAVES ARE NO LONGER NEGATIVE IN THE LEFT PRECORDIAL LEADS AND THERE HAVE BEEN ONLY MINOR ST/T CHANGES IN THE LATERAL LEADS.

CONCLUSIONS
1) EVIDENCE FOR LVH PERSISTS.
2) PERSISTING LEFT AXIS DEVIATION. ANTERIOR FASCICULAR BLOCK.
3) THE ST/T CHANGES SUGGEST REGRESSION OF AN ISCHEMIC PROCESS, WHICH MUST BE CONFIRMED CLINICALLY.

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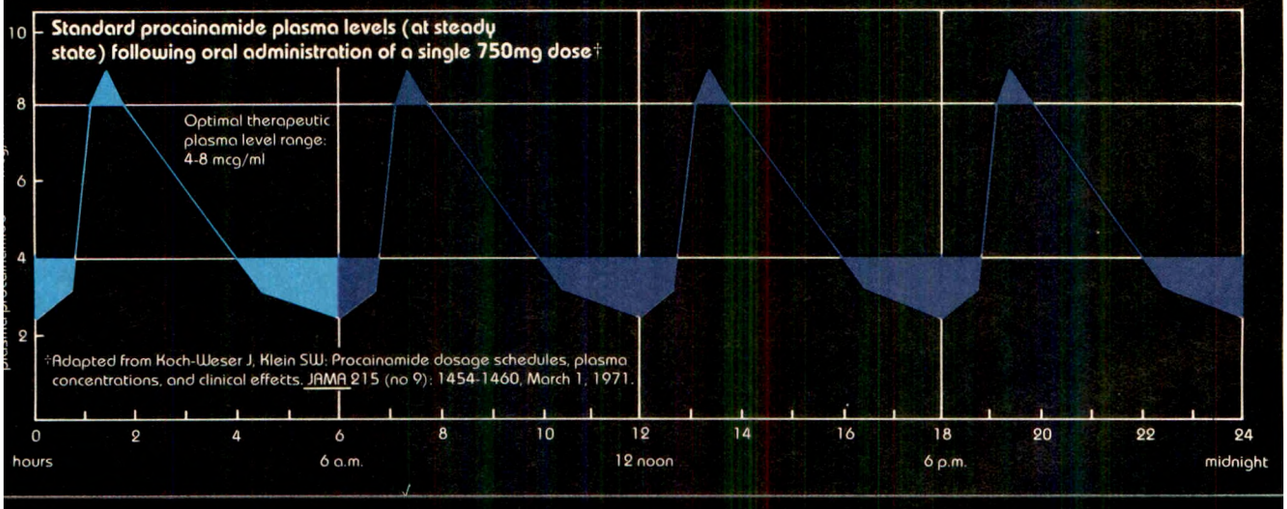
Procan™ SR

(PROCAINAMIDE HYDROCHLORIDE TABLETS)

therapeutic gap exists when
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t greater than 3 hour intervals

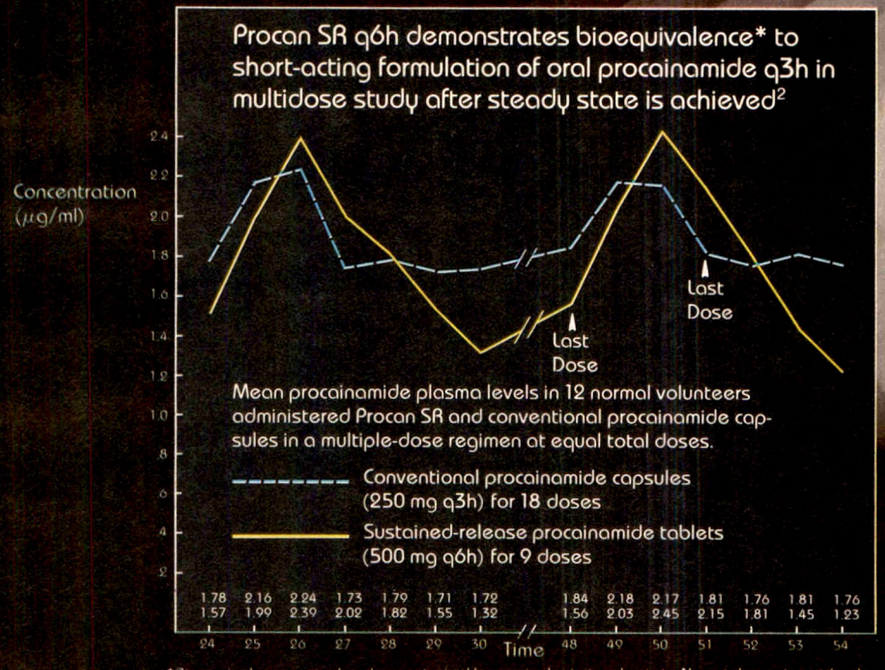
Adequate blood levels maintained only 2/3 of the
me during a 6 hour dosing interval

Patient control may be threatened



"To avoid unacceptable fluctuations
the plasma levels of procainamide, the oral
reparation available at present has to be
iven at 3 h intervals . . . .[1]"

Bioequivalence of PROCAN SR to conventional procainamide capsules demonstrated in multi-dose study[2]



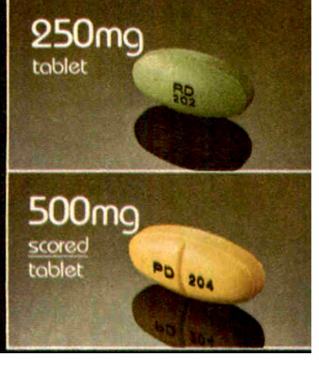
*Bioequivalence was also demonstrated by equivalent steady-state N-acetylprocainamide plasma levels, by equivalent procainamide steady-state urinary excretion, and by equivalent total procainamide 0 to 96 hour urinary excretion (58.7% of procainamide doses were excreted in urine with PROCAN SR, compared with 60% for conventional procainamide capsules).

for selected cardiac dysrhythmias

- Cuts the dosing frequency of conventional oral procainamide therapy **in half**
- Promotes better patient **compliance**
- Helps eliminate the therapeutic gap and maintains blood levels **all day** and **all night**

- Formulated using a special wax matrix — perm slow dissolution

2 strengths for greater flexibility



Procan™ SR

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SUSTAINED RELEASE

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

DESCRIPTION

Procainamide hydrochloride is the amide analogue of procaine hydrochloride. Each tablet of Procan SR contains procainamide hydrochloride in a tablet matrix specially designed for the prolonged release of the drug in the gastrointestinal tract. Procan SR is available for oral administration as green, film-coated tablets containing 250 mg procainamide hydrochloride and as yellow, film-coated tablets containing 500 mg procainamide hydrochloride.

ACTION

Procainamide depresses the excitability of cardiac muscle to electrical stimulation, and slows conduction in the atrium, the bundle of His, and the ventricle. The refractory period of the atrium is considerably more prolonged than that of the ventricle. Contractility of the heart is usually not affected nor is cardiac output decreased to any extent unless myocardial damage exists. In the absence of any arrhythmia, the heart rate may occasionally be accelerated by conventional doses, suggesting that the drug possesses anticholinergic properties. Larger doses can induce atrioventricular block and ventricular extrasystoles which may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram; a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

The sustained-release characteristic of Procan SR tablets has been demonstrated in studies in human subjects. A multiple-dose study has shown equivalent steady-state plasma levels of Procan SR tablets given every six hours when compared with an equal total daily dose of Pronestyl® (procainamide hydrochloride capsules, E.R. Squibb and Sons) given every three hours.

Procainamide is less readily hydrolyzed than procaine, and plasma levels decline slowly — about 10 to 20% per hour for standard dosage forms of procainamide. The drug is excreted primarily in the urine, about 10% as free and conjugated p-aminobenzoic acid, and about 60% in the unchanged form. The fate of the remainder is unknown.

INDICATIONS

Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS

During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs'-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

ADVERSE REACTIONS

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS). Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION

Procan SR tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every three hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia — Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dosage of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia — Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dosage of 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED

N 0071-0202 Procan SR 250 mg. Each sustained-release tablet contains 250 mg procainamide hydrochloride. Available in bottles of 100 tablets.

N 0071-0204 Procan SR 500 mg. Each sustained-release, scored tablet contains 500 mg procainamide hydrochloride. Available in bottles of 100 tablets.

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2. Data on file, Medical Affairs Dept., Pharmaceutical Division, Warner-Lambert Co.

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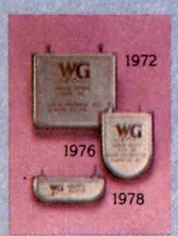
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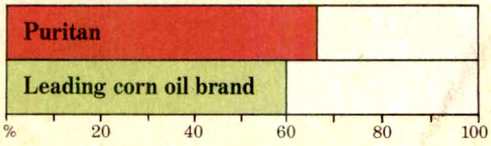
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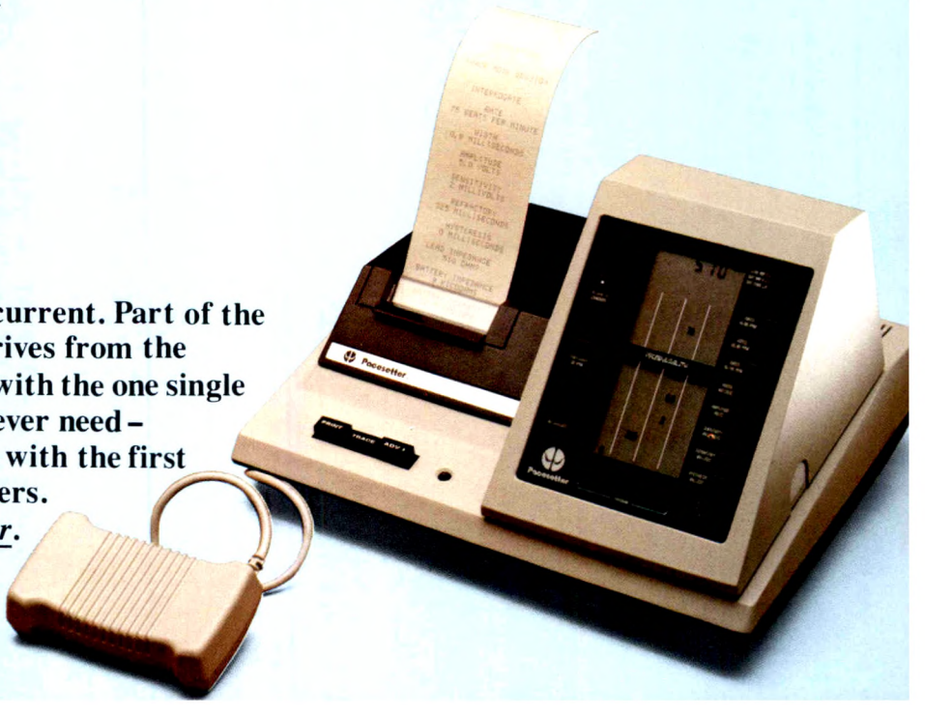


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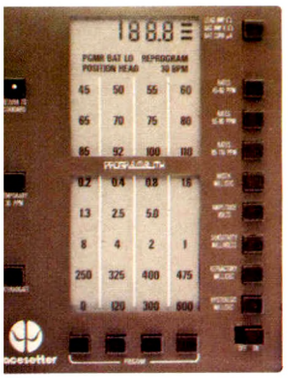
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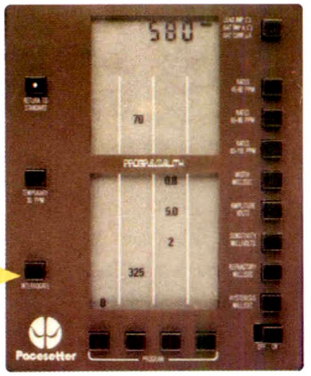


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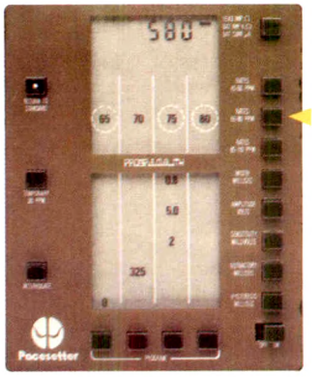
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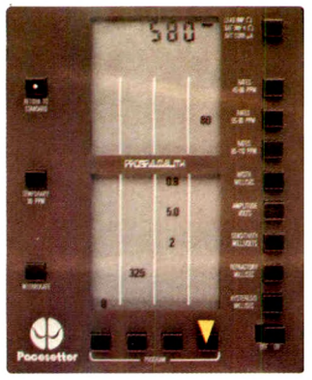
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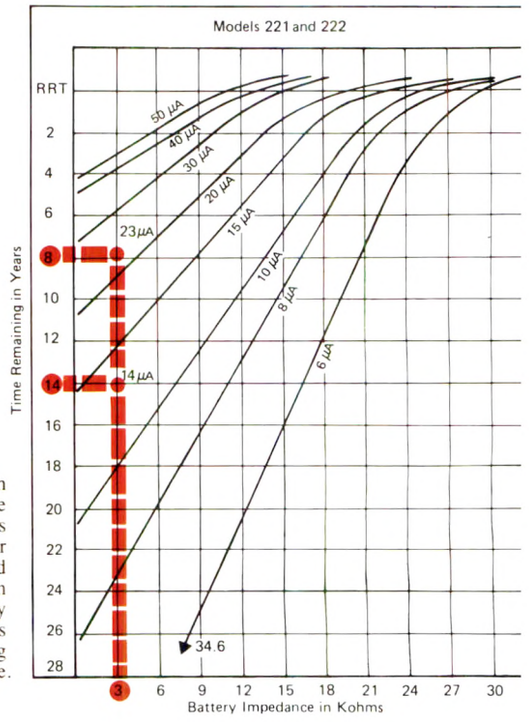
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Congenital Hypoplasia of Portions of Both Right and Left Ventricular Myocardial Walls

Clinical and Necropsy Observations in Two Patients With Parchment Heart Syndrome

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Clinical and morphologic findings are described in two patients with congenital hypoplasia of portions of both right and left ventricular free walls in the absence of associated coronary or valvular heart disease. One, a 61 year old man who had never had clinical evidence of cardiac dysfunction, died suddenly and unexpectedly. The second, a 55 year old woman, died of progressive, eventually intractable congestive heart failure of 29 months' duration. Although at least 22 necropsy patients have previously been reported to have "parchment-like" thinning of portions of the right ventricular free wall, only one patient has previously been described with such thinning of portions of both right and left ventricular free walls. The spectrum of right or right and left ventricular wall congenital hypoplasia is a broad one, with nearly half of described patients dying of congestive heart failure in the 1st year of life and the other half reaching adulthood with or without manifestations of cardiac dysfunction.

Partial to near complete absence of right ventricular myocardium ("parchment heart") with normal cardiac valves and normal or near normal coronary arteries has been reported in at least 22 necropsy patients (Table I),[1–22] only one of whom had associated thinning of the left ventricular free wall. In the report that follows, cardiac findings are described in two patients who had localized thinning of portions of both right and left ventricular free walls unassociated with coronary narrowing or abnormal cardiac valves. In addition, cardiac findings are summarized in previously described patients with the "parchment heart."

Description of Patients

Case 1

This was a 61 year old black man who died in August 1978. He had been well until the day of death when he complained of abdominal pain after consuming large quantities of alcohol the preceding day. While at home, he suddenly raised his arms, gasped for breath, collapsed and was dead. He had never had symptoms of cardiac dysfunction. A brief examination 5 years before death, at the time of a minor head injury, disclosed his blood pressure to be 130/70 mm Hg. No cardiac abnormalities were detected on precordial examination.

Necropsy findings: The heart weighed 350 g. A portion of the anterior wall of the right ventricular outflow tract was thin (Fig. 1) and histologic study revealed few myocardial fibers (Fig. 2). A similar area of thinning that bulged involved the apical portion of the left ventricle (Fig. 1). The wall of the thinned left ventricular apex contained a few myocardial fibers (Fig. 3). The four major epicardial coronary arteries (right, left main, left anterior descending and left circumflex) were virtually free of atherosclerotic plaque.

Case 2

This 55 year old white woman, who died in December 1979, had been well until July 1977 when she noted exertional epigastric distress, easy fatigability and,

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TABLE I

Clinical and Morphologic Observations in 22 Previously Described Necropsy Patients With Parchment Hearts

Reference													Location of Absent Ventricular Myocardium								
													RV					Thrombus		Defect of AS	
First Author	Year	Age at Death	Sex	CHF	P	Duration Sy (mo)	C	M	CE (X-Ray)	Abnl ECG	Mode of Death	HW (g)	I	A	O	VS	LV	RV	LV	PFO	S
Patients Aged 5 Years or Less																					
Haworth[1]	1975	1 day	M	+	–	1 day	+	+	+	+	CHF	–	+	+	0	–	–	0	0	+	0
Diaz[2]	1973	4 mo	M	+	–	4	+	0	+	+	CHF	–	+	0	0	–	0	0	0	0	0
Novak[3]	1957	5 mo	M	+	–	5	+	0	+	+	CHF	–	+	+	0	–	0	0	0	+	0
Arcilla[4]	1961	6 mo	M	+	–	6	0	+	+	+	CHF	–	+	+	+	–	0	0	0	+	0
Uhl[5]	1952	7 mo	F	+	–	4	+	0	+	+	CHF	–	+	+	0	–	0	+	0	0	0
Cumming[6]	1965	7 mo	F	+	–	4	0	–	+	+	PO	48	0	+	0	–	0	0	0	+	0
Aherne[7]	1973	7 mo	F	+	–	3	0	–	+	+	CHF	–	+	+	+	–	0	0	0	0	0
Perrin[8]	1965	10 mo	M	+	–	7	+	+	+	+	CHF	–	0	+	0	–	0	–	–	0	0
Sherman[9]	1963	15 mo	F	+	–	12	+	0	+	+	CHF	–	+	+	+	–	0	–	–	0	0
Kinare[10]	1969	60 mo	F	+	0	60	+	0	+	+	CHF	130	+	+	+	–	0	0	0	0	0
Patients Aged More Than 15 Years																					
Abe[11]	1973	17 yr	F	+	0	48	0	0	+	+	PO	400	0	+	+	–	0	0	0	0	0
Murata[12]	1976	18 yr	F	+	0	12	0	0	+	+	CHF	400	0	+	+	–	0	+	0	0	0
Froment[13]	1968	19 yr	M	+	0	–	0	–	+	–	CHF	350	0	+	0	–	–	+	–	–	–
Vecht[14]	1979	19 yr	M	+	+	132	+	–	+	+	PO	435	+	0	0	–	–	0	0	0	+
Castleman[15]	1952	24 yr	F	+	0	12	0	+	+	+	CHF	300	+	+	+	–	0	+	0	0	0
Froment[13]	1968	26 yr	M	+	0	–	0	–	+	–	CHF	430	0	+	0	–	–	+	–	–	–
Bharati[16]	1978	29 yr	F	+	0	108	0	0	+	+	CHF +CHB	545	+	+	+	+	0	+	0	0	0
Osler[17] / Segall[18]	1905 / 1950	"40's"	M	–	–	–	–	–	–	–	SD	168	+	+	+	–	+	0	0	0	0
Reeve[19]	1964	47 yr	F	+	+	432	+	+	+	+	CA	290	+	0	0	–	0	0	0	+	0
Forssman[20]	1972	47 yr	M	0	–	–	0	–	–	+	SD	–	0	+	0	0	–	–	–	–	–
Gould[21]	1967	66 yr	M	0	0	0	0	0	0	0	L	600	+	+	0	–	0	–	–	0	0
Sugiura[22]	1970	84 yr	F	0	0	0	0	0	0	0	AP	220	0	0	+	–	0	0	0	0	0

A = ventricular apex; Abnl = abnormal; AP = acute pneumonia; AS = atrial septum; C = cyanosis; CA = cerebrovascular accident; CE = cardiac enlargement; CHB = complete heart block; CHF = congestive heart failure; ECG = electrocardiogram; HW = heart weight; I = inflow tract; L = leukemia; LV = left ventricle; M = precordial murmur; O = outflow tract; P = chest pain; PFO = patent foramen ovale; PO = early postoperatively; RV = right ventricle; S = secundum; SD = sudden death; Sy = symptoms of cardiac dysfunction; VS = ventricular septum; – = no information available; + = present or positive; 0 = absent or negative.

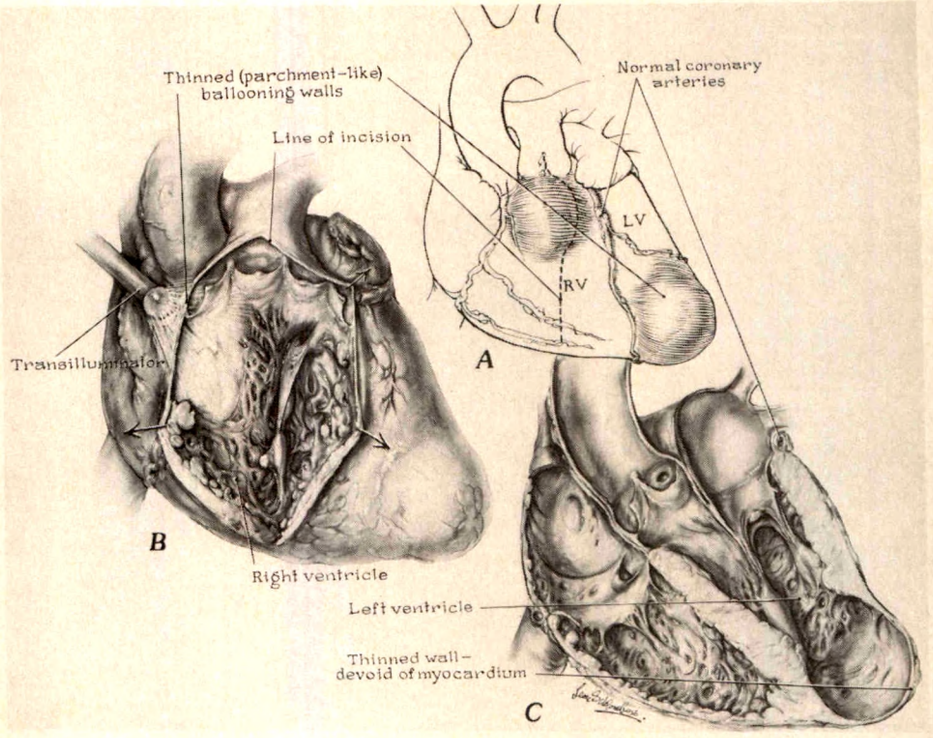


FIGURE 1. Case 1. Drawings of the heart showing the thinned portions of myocardium of the right ventricular outflow tract and left ventricular apex. LV = left ventricle; RV = right ventricle.

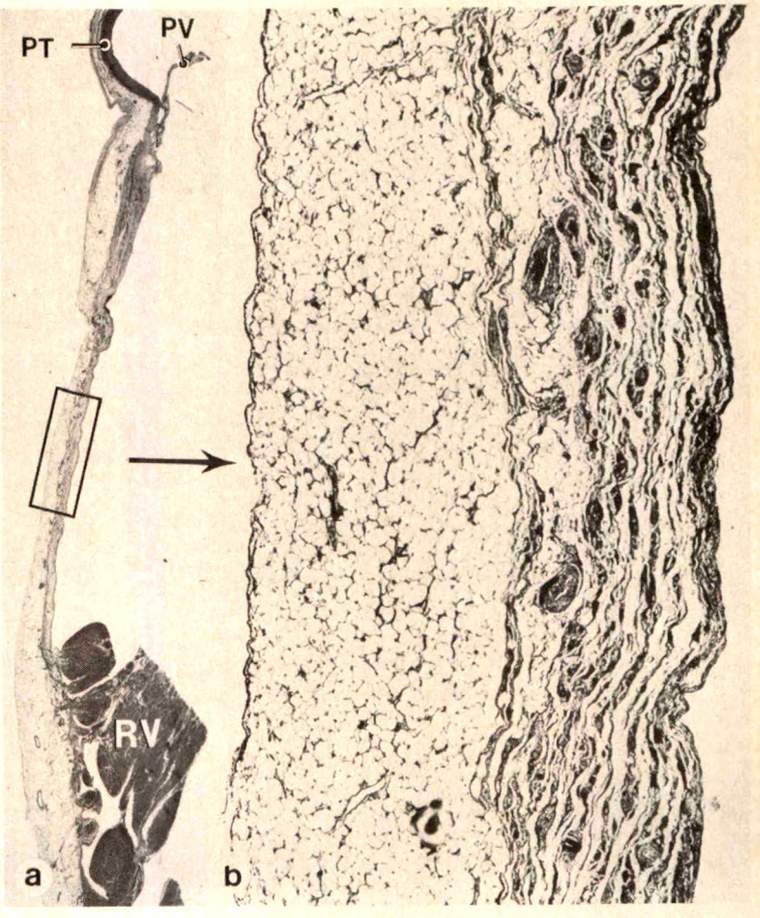


FIGURE 2. Case 1. Photomicrographs of the thinned right ventricular outflow tract. Lower power view (**a**) and higher magnification view (**b**) of the boxed area, showing a few myocardial fibers. PT = pulmonary trunk; PV = pulmonary valve; RV = right ventricle. (Movat stain ×4 [**a**] and ×55 [**b**], both reduced by 20 percent.)

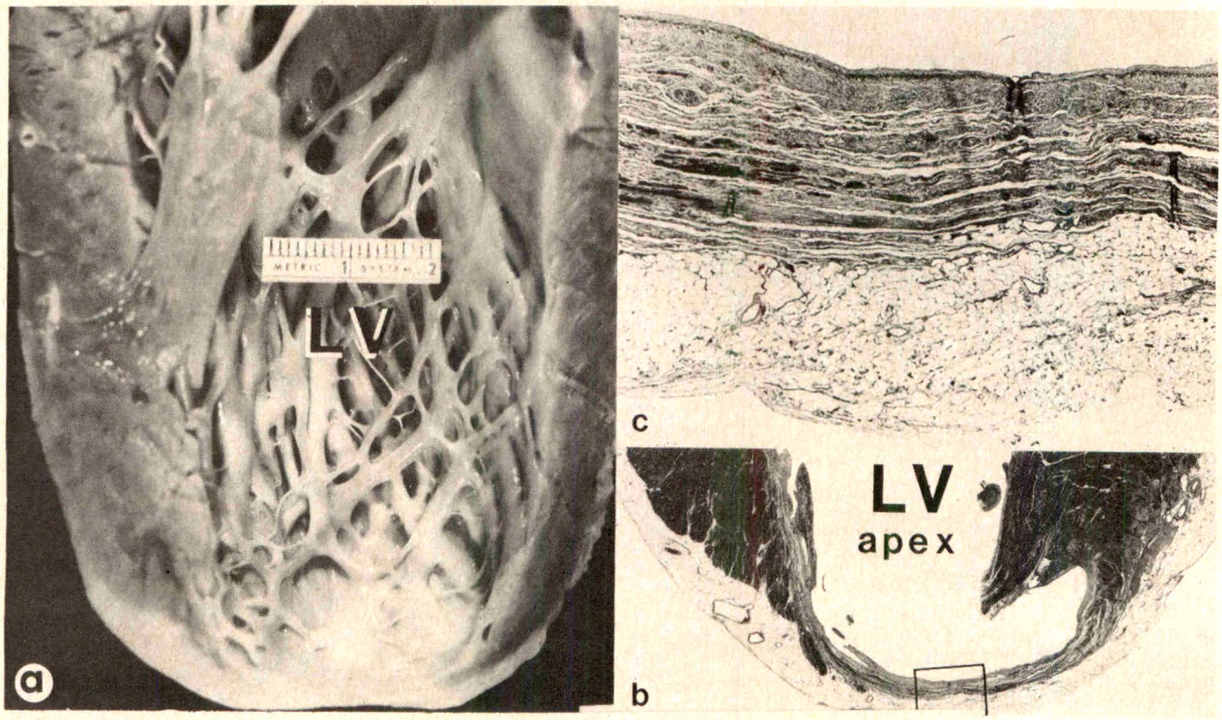


FIGURE 3. Case 1. Opened left ventricle (LV) showing the thinned apical portion (**a** and **b**). A close-up of the **boxed area** in **b** is shown in **c**. Relatively few myocardial fibers remain. (Movat stains ×10 [**b**], and ×55 [**c**], both reduced by 20 percent.)

subsequently, swelling of her abdomen and legs. She had exertional dyspnea but no orthopnea or nocturnal dyspnea. Diuretic therapy provided little improvement. On examination in February 1978, she was 157.5 cm tall, weighed 54 kg, and the blood pressure was 115/80 mm Hg without significant paradox. The venous pressure was markedly elevated with a rapid diastolic collapse. A right ventricular impulse was palpated and a third heart sound and soft pansystolic murmur of maximal intensity at the cardiac apex were audible. The liver and spleen were enlarged, tense ascites was evident and the legs were edematous. The chest was clear.

Laboratory findings: Hematologic and biochemical investigations were normal except for slight degrees of hypoalbuminemia and hyperbilirubinemia. A chest roentgenogram

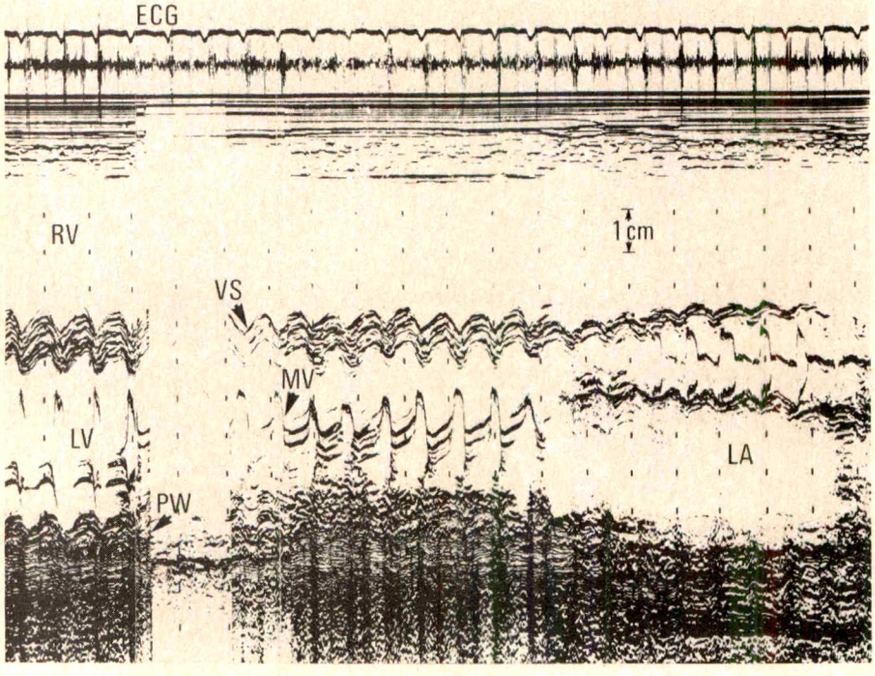


FIGURE 4. Case 2. Echocardiogram showing a scan from the aorta (**at right**) to the left ventricular (LV) cavity (**at left**). The right ventricle (RV) is dilated and the ventricular septum (VS) moves paradoxically (**arrow**). The posterobasal left ventricular free wall (PW) appears thinner than the septum and is hypokinetic. The left atrium (LA) is slightly dilated. MV = mitral valve.

disclosed cardiomegaly and clear lungs. An electrocardiogram revealed sinus rhythm, occasional supraventricular ectopic complexes, low voltage, incomplete right bundle branch block and changes compatible with old posterior myocardial infarct. An echocardiogram (Fig. 4) showed an enlarged right ventricle with paradoxical septal movement, a slightly enlarged left atrium and a thinned and hypokinetic posterobasal left ventricular free wall.

On cardiac catheterization, the cardiac pressures (in mm Hg) were: pulmonary artery, 28/20; right ventricle, 28/15 (mean 21); right atrial *a* wave, 22, v wave, 28 and mean, 22 (Fig. 5); left ventricle, 120/0 and aorta 120/65. The left ventriculogram disclosed a normal-sized chamber, an ejection fraction of 64 percent, akinesia of the posterobasal wall, and slight mitral regurgitation. Selective coronary arteriography revealed normal arteries. The right ventriculogram showed a dilated cavity with hypokinesia, most marked in the posterobasal and outflow portions.

Operative findings and course: To rule out pericardial disease, the patient underwent thoracotomy in March 1978. The pericardial layers were normal, and the sac contained 300 to 400 ml of serous fluid. The right atrial wall was hypertrophied; the right ventricle was dilated and contracted poorly. In several areas the right ventricular wall was extremely thin.

Postoperatively, the marked fatigue persisted. By August 1978, further cardiomegaly by roentgenogram and a right pleural effusion (transudate) were evident. In November 1979 she was rehospitalized with anasarca, oliguria and hypotension. She died in December 1979 from intractable heart failure complicated by atrial and ventricular arrhythmias.

Necropsy findings: The heart weighed 320 g. The wall of the right ventricular outflow tract and apex was "paper thin" and contained few myocardial fibers (Fig. 6). The posterobasal portions of both right and left ventricular free walls also were thinned, but more myocardial fibers surrounded by fibrous tissue were present in this portion of right ventricular free wall and a layer of myocardium was present beneath the endocardium in the thinned portion of left ventricular free wall. The right atrium, right ventricle and tricuspid valve anulus (12.5 cm in circumference) were dilated and the right atrial wall was hypertrophied. Several mural thrombi were present in the right ventricle and right atrium. All major coronary arteries were free of atherosclerotic plaques.

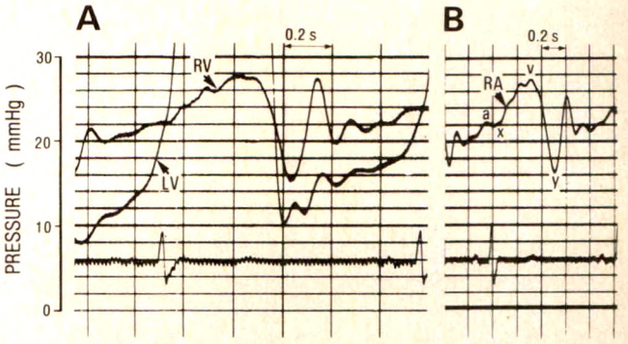


FIGURE 5. Case 2. **A,** simultaneous left ventricular (LV) and right ventricular (RV) pressures. The right ventricular end-diastolic pressure is elevated and the dip-end-plateau configuration in early diastole is present. **B,** high right atrial (RA) pressure with rapid y descent.

Comments

Each of these two patients had severe thinning of portions of the right and left ventricular free walls and each had normal coronary arteries and normal cardiac valves. One, a 61 year old man, had been asymptomatic all his life and died suddenly, and at necropsy the only abnormality was the localized deficiency of ventricular myocardium. The second patient, a 55 year old woman, had been asymptomatic until age 53 when congestive heart failure appeared; it became intractable and eventually fatal. The latter patient had a much larger loss of right ventricular myocardium than did the former patient; the amount of deficient left ventricular myocardium was roughly similar in each, although located at different sites.

Previously reported cases of thinning of the right ventricular wall: Osler[17] in 1905 was the first to describe a patient with "parchment-like" thinning of a ventricular wall in the absence of coronary or valve disease. His patient was believed to be a man in his 40s who died suddenly and unexpectedly while walking up

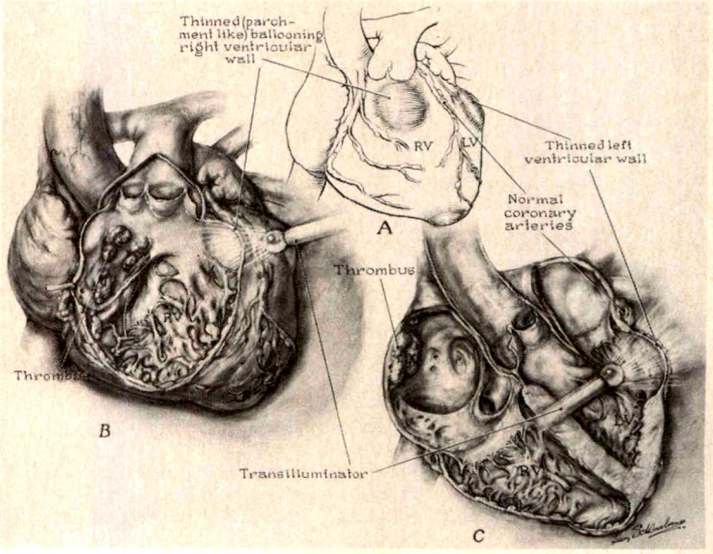


FIGURE 6. Case 2. Drawings of the heart showing thinned portions of right (RV) and left ventricular (LV) walls. Thrombi are present in the right atrial and right ventricular cavities.

a hill. At necropsy, the localized thinning involved portions of both ventricular walls as was the case in our two patients. Segall[18] in 1950 described in more detail the patient briefly referred to by Osler in the 1905 edition of his textbook. The second patient reported to have a parchment-like heart was a 23 year old woman who had chronic, eventually fatal congestive heart failure for nearly 1 year. This patient, reported on in May 15, 1952 in *The New England Journal of Medicine*,[15] was similar to our Patient 2. The third patient was described in 1952 by Uhl.[5] His patient was a 7 month old girl who had evidence of severe right-sided congestive heart failure and severe thinning of most of the right ventricular wall. Uhl's paper was entitled: "A previously undescribed congenital malformation of the heart: almost total absence of the myocardium of right ventricle." Since his report most authors describing patients with "parchment-like" thinning of the wall of right ventricle have referred to this condition as "Uhl's anomaly." It is true that Uhl was the first to describe a child with a parchment-like right ventricular wall, but he was preceded in describing this condition by Osler,[17] Segall,[18] and Castleman and Sprague[15] whose publications on this subject were overlooked by Uhl. Because Osler's description appeared only in a textbook, it is understandable how his description could have been missed. Overlooking Segall's report or possibly Castleman and Sprague's clinicopathologic conference in *The New England Journal of Medicine* is less understandable. We believe it best to eliminate the eponym for this condition, which we prefer to call "congenital hypoplasia of ventricular myocardium."

Clinical features: Since 1952, at least 21 additional patients with parchment-like thinning of portions of right ventricular free wall have been reported[1–22] (Table I). Surprisingly, the myocardial thinning in each was limited to the right ventricular wall and none had involvement of both ventricular free walls as did our two patients. One,[16] however, also had thinning of the ventricular septum. The described patients fall neatly into two age groups: those aged 5 years and younger[1–10] and those over age 15 years.[11–22] Of the 22 previously described patients, 8 were under age 1 year,[1–8] 1 was 15 months old,[9] 1 was 5 years old[10] and the remaining 12 patients were 17 to 84 years old.[11–22] In all 10 patients aged 5 years and under, congestive heart failure was clinically evident from birth and it became intractable and fatal. Of the 12 patients over age 15 years, 8 had chronic congestive heart failure, which was the cause of death in 5. Not all patients with parchment-like thinning of the right ventricular wall in the absence of coronary and valve disease have congestive heart failure or other clinical evidences of cardiac dysfunction. The 66 year old man reported on by Gould et al.[21] and the 84 year old woman reported on by Sugiura et al.[22] never had evidence of cardiac dysfunction and died from noncardiac conditions. Two of the older patients, as did our Patient 1, died suddenly.[17,18,20]

Hemodynamic and angiographic features: Hemodynamic studies have been reported in 6[4,6,11,12,14,16] of the 22 previously described patients and in 1 of our 2 patients. All seven had normal pulmonary arterial and right ventricular systolic pressures. However, the right ventricular end-diastolic pressure, (measured in six patients, was elevated in each (range 12 to 22 mm Hg). The right atrial pressure (measured in six patients)[4,6,11,12,14] was also elevated in each, with the mean pressure ranging from 8 to 28 mm Hg. In all but one patient,[16] the pulmonary arterial and right ventricular end-diastolic and right atrial mean pressures were the same or nearly the same. In our Patient 2, the similarity of these three pressures led to thoracotomy to rule out pericardial constriction. This patient was the only one of the seven patients who also had determination of left ventricular pressures, which were normal. Cardiac index (measured in three patients)[4,6,16] was severely depressed (1.3, 1.7, and 1.8 liters/min per m^2, respectively). Thus, parchment-like thinning of the right ventricular wall may cause equalization of pulmonary arterial, right ventricular end-diastolic and mean right atrial pressures and severe depression of cardiac output. Right ventricular angiography performed in five of the seven patients,[4,6,12,14] disclosed poor contractility of the ventricle in each, dilatation of this chamber in each with or without localized aneurysmal formation and focal or diffuse thinning of its wall, tricuspid valve regurgitation in one,[16] and right atrial dilatation in three patients.[4,6,12]

Differential diagnosis: Clinically, the differential diagnosis of congenital hypoplasia of the right ventricular myocardium includes Ebstein's anomaly of the tricuspid valve, idiopathic dilated cardiomyopathy and pulmonary or tricuspid valve atresia. The echocardiogram is useful in distinguishing congenital hypoplasia of the right ventricular myocardium from Ebstein's anomaly[20] by the presence of a dilated right ventricular cavity (as in our Case 2), delayed tricuspid valve closure, and diastolic opening of the pulmonary valve in patients with the former.[23] Angiographically, dilatation of the right ventricular cavity may not be useful in differentiating idiopathic dilated cardiomyopathy from congenital hypoplasia of the right ventricular myocardium, but the presence of left ventricular dilatation obviously favors the diagnosis of cardiomyopathy.

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Biventricular Hypoplasia With Myocardial Fiber Hypertrophy and Disarray

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Birmingham, Alabama

A 25 year old woman with effort intolerance and systemic venous congestion since childhood, and restrictive ventricular filling and severe atrioventricular (A-V) valve regurgitation at cardiac catheterization died after valve replacement surgery. At autopsy, the atria were enlarged and thickened; both ventricles were small. In some areas the right ventricular wall was only a few myofibers thick. The myofibers of both ventricles were hypertrophied, and there was widespread fiber disarray in the left ventricular free wall, the interventricular septum and, focally, the right ventricular free wall. Because the ventricles were not enlarged or thickened despite myocardial fiber hypertrophy and severe chronic A-V valve regurgitation, and the myofiber disarray was widespread, this is a very unusual case of biventricular hypoplasia and dysplasia.

In this report we describe an unusual case of cardiac biventricular hypoplasia and dysplasia with restrictive ventricular dysfunction, atrioventricular (A-V) valve incompetence and marked enlargement of the atria. Although the right ventricle was thinned to only a few myofibers in some areas, it contained functioning myocardium,[1,2] and thus this case differs from Uhl's anomaly. Despite histologic evidence of hypertrophic cardiomyopathy[3–9] and severe chronic A-V valve regurgitation, the ventricles were not enlarged or thickened and are thus considered hypoplastic.

Case Report

A 25 year old white woman had dyspnea and fatigue from early childhood. Initial cardiac catheterization at age 6 years revealed the following pressure measurements (in mm Hg): pulmonary capillary wedge 20, pulmonary arterial 35/20 and right ventricular 35/6. Systemic arterial oxygen saturation was 98 percent. Reevaluation at age 21 years because of syncope and venous congestion disclosed a large pericardial effusion. Removal of 825 ml of pericardial fluid by pericardiocentesis produced a transient decrease in systemic venous congestion but did not reveal the cause of the effusion. Two months later, because of the possibility of recurrent pericardial effusion, a median sternotomy was performed. The right atrium was found to be grossly enlarged and thickened. The right ventricle was described as smaller than normal. Biopsy of the pericardium yielded normal findings. Although only a small amount of pericardial fluid was present, a pericardial window was created into the right pleural space. Postoperative cardiac catheterization revealed the following pressure measurements (in mm Hg): left ventricular 100/20, pulmonary arterial 38/25, right ventricular 38/18 and mean right atrial 18. Although the patient was treated with digitalis and several antiarrhythmic agents, she had multiple episodes of atrial tachycardia and atrial flutter with variable atrioventricular (A-V) block. Recurrent syncope and one documented episode of 4:1 A-V block prompted placement of a right ventricular endocardial demand pacemaker. Because of progressive systemic venous congestion and marked effort intolerance unresponsive to treatment with digitalis and diuretic agents, she was referred to the University of Alabama Medical Center.

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Clinical findings: On physical examination, she was a thin, chronically ill woman weighing 45 kg with peripheral cyanosis and no clubbing. Heart rate was 74 beats/min; blood pressure 90/60 mm Hg; respiratory rate 20/minute. There was mild lumbar scoliosis. The lungs were clear. The jugular venous pressure was elevated with a prominent *v* wave. There was no palpable apical impulse, but there was a left parasternal impulse. The first heart sound was accentuated and the second heart sound was closely split and accentuated in the pulmonary area. There was a prominent third sound, a grade 1/6 diastolic rumble at the left sternal border that increased with inspiration, and a grade 2/6 pansystolic murmur at the left sternal border and the apex. The liver was enlarged, palpable 4 cm beneath the right costal margin. There was mild peripheral edema.

The electrocardiogram revealed atrial tachycardia with 2:1 A-V block and right ventricular conduction delay. Hematocrit was 41 percent. A thallium-201 perfusion scan at rest showed both ventricles to be small with uniform uptake of radionuclide.

Cardiac catheterization demonstrated the following pressures (in mm Hg): right atrial 18 (*v* wave 25); right ventricular 35/18, pulmonary arterial 35/18, pulmonary capillary wedge 18 (*v* wave 35), left ventricular 105/18 and aortic 105/69. Simultaneous measurements of right and left ventricular pressures showed end-diastolic equalization with an early diastolic dip and a mid and late diastolic plateau (Fig. 1). Arterial oxygen saturation was 97 percent, and the cardiac index, obtained with the Fick method was 1.17 liter/min per m^2.

Biplane right and left ventricular cine angiography (Fig. 2) demonstrated intact atrial and ventricular septa. The small left ventricle (end-diastolic volume 56 ml/m^2) had a normal contraction pattern but there was severe mitral regurgitation into an enlarged left atrium. Similarly, the right ventricle was small (end-diastolic volume 69 ml/m^2) with mildly diminished contraction. The tricuspid valve was in the normal position and severely incompetent. The right atrium was enormously enlarged. Early in diastole, the ventricles expanded rapidly but without further filling during the latter two thirds of diastole.

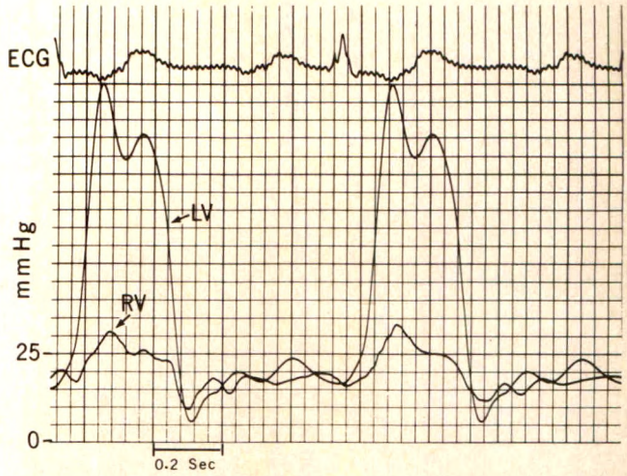


FIGURE 1. Simultaneously recorded left (LV) and right ventricular (RV) pressures show a diastolic dip and plateau pattern with late diastolic equalization of pressures. ECG = electrocardiogram.

Operation: The preoperative diagnosis was severe tricuspid and mitral regurgitation with restrictive ventricular physiology due, it was hoped, to surgically resectable subendocardial fibrosis or pericardial constriction. At operation the pericardium was normal. Both atria were severely enlarged,

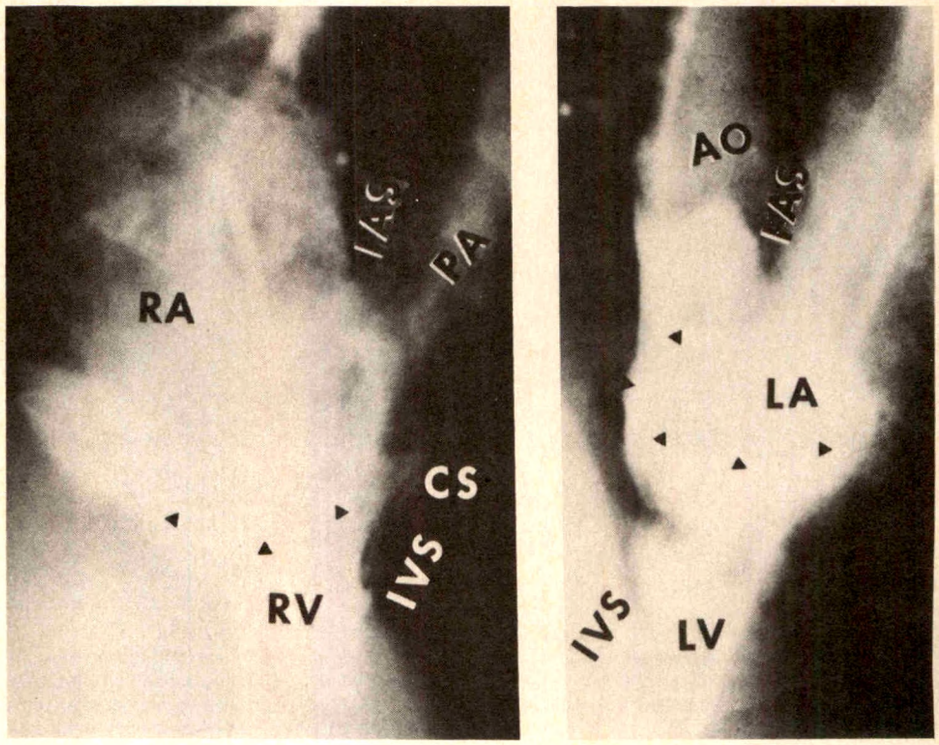


FIGURE 2. Right (RV) and left ventricular (LV) angiograms in the 45° left anterior oblique, 30° cranial projection. The levels of the tricuspid (**left**) and mitral (**right**) valve anuli are shown with **triangles**. Both ventricles are small in comparison with the enlarged right (RA) and left (LA) atria. AO = aorta; CS = coronary sinus; IAS = interatrial septum; IVS = interventricular septum; PA = pulmonary artery.

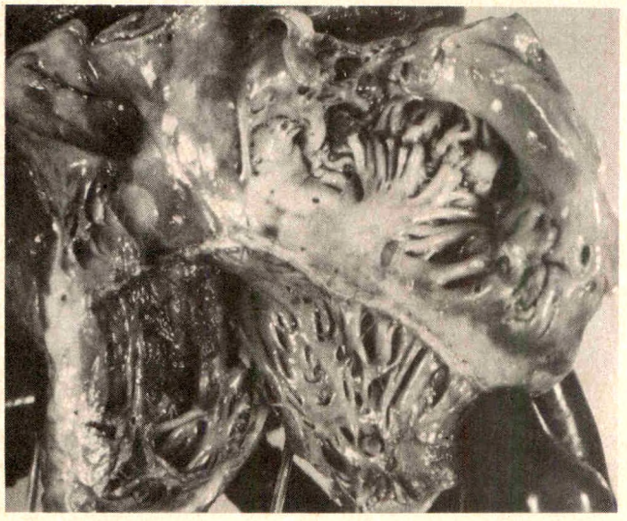


FIGURE 3. Gross photograph of right atrium and right ventricle. The right atrium (**top**) is greatly enlarged and shows a diffusely thickened endocardium. The tricuspid valve has been removed surgically. The right ventricle is small. The denuded area on the interventricular septum (**left**) is where the endocardium had been surgically removed. (X1, reduced by 38 percent.)

the ventricles were small and there was no subendocardial fibrosis. A focal area of endocardial thickening in the interventricular septum of the right ventricle was removed. The mitral and tricuspid valve tissue appeared normal, although the valves were severely incompetent. They were resected and replaced with heterograft valves. Although intensive support was given, the patient died soon after operation.

Autopsy: Abnormalities in the postmortem examination were limited to the liver and heart. The liver showed marked fibrosis suggesting cardiac cirrhosis. The heart weighed 275 g. Both atria were greatly enlarged with hypertrophied muscular walls and diffuse endocardial thickening. The ventricles were small. The right and left ventricular endocardium appeared normal except for the denuded area in the right ventricular inlet septum where thickened endocardium had been surgically removed. The tricuspid anulus was dilated, measuring 13 cm in circumference (Fig. 3). The right ventricular wall thickness was normal (3 mm); however, there were deep recesses between trabeculae carneae producing very thin areas in the right ventricle. Histologic sections (Fig. 4) of the right ventricle showed numerous focal areas of fiber disarray and deep recesses of the ventricular cavity into the myocardium with the wall only a few myofibers thick. Myofibers in the right and left ventricles were hypertrophied as evidenced by their width and the presence of large hyperchromatic nuclei and binucleated fibers. The left ventricular maximal wall thickness was 8 mm. The interventricular septum was not thickened and the mitral anulus was dilated, measuring 11 cm in circumference. The left ventricular muscle histologically showed widespread fiber disarray (Fig. 5). Neither ventricle manifested an increase in interstitial fibrous tissue. The semilunar valves, coronary arteries, specialized conduction tissue and resected A-V valves were normal.

Comments

This young woman had cardiac symptoms and abnormal intracardiac pressures from early childhood. By her early 20s, her exercise tolerance was severly impaired by systemic venous congestion and greatly reduced cardiac output. The hemodynamic findings were those of restrictive cardiomyopathy with equalization of diastolic pressures, a ventricular diastolic dip and plateau pattern, and cessation of ventricular filling after the first third of diastole. The ventricles were small, much smaller than would be expected with severe chronic tricuspid and mitral regurgitation. The cause of the pericardial effusion present 4 years before death is not clear, but subsequently the pericardium was



FIGURE 4. Photomicrograph of right ventricle; epicardium is at **top**. Clear spaces at **bottom** and **middle** of micrograph are recesses of the ventricular lumen. Right ventricular wall, adjacent to epicardial fat, is thinned to as few as two myofibers in some areas. (Gomori trichrome X460, reduced by 29 percent.)

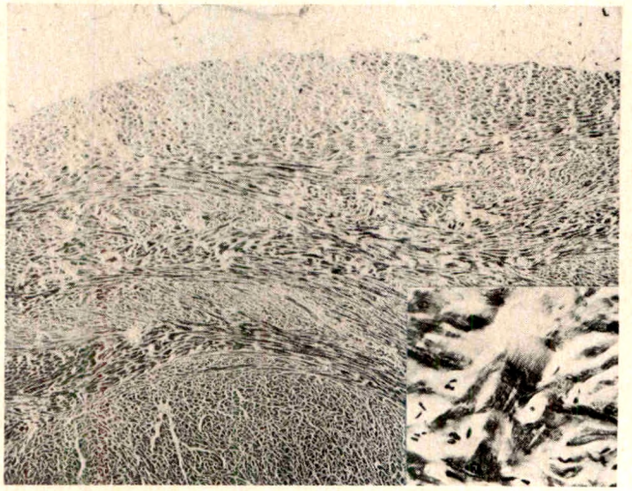


FIGURE 5. Photomicrograph of left ventricle, anterior free wall, horizontal section; epicardium is at **top**. Myofibers show an interlacing fascicular pattern. Inset at **lower right** shows marked fiber disarray found in interventricular septum. (Gomori trichrome X310 [inset X690], reduced by 29 percent.)

normal and was not contributing to the hemodynamic abnormalities before death.

Congenital hypoplasia of both ventricles: The unusual autopsy findings of a very thin-walled right ventricle with hypertrophied disordered fibers and a small left ventricle with marked fiber disarray and hypertrophy suggest that the underlying problem was congenital hypoplasia of the ventricles. We believe that the congenitally small and dysplastic ventricles had hypertrophied and dilated to their maximal extent and, despite severe chronic A-V valve incompetence, had not increased to even average size. The small ventricles with decreased ventricular compliance, probably due to extensive myofiber disarray, resulted in the restrictive physiology. The increased resistance to ventricular filling led to atrial and A-V valve anular dilation, resulting in mitral and tricuspid regurgitation that further enlarged the atria. The marked atrial overload predisposed the patient to atrial arrhythmias. The small dysplastic ventricles were unable to maintain an adequate forward cardiac output.

This condition has not previously been reported. The right ventricular hypoplasia differs from Uhl's anomaly in which there is absence of right ventricular myocardium.[1,2] Our patient's right ventricle, although quite thin in some areas, did contain functioning myocardium and did contract. In Uhl's anomaly, the right ventricle without functioning myocardium forms a passive conduit from the actively pumping right atrium to the pulmonary circulation.[2]

Left ventricular fiber disarray or dysplasia: Our patient also had an abnormal left ventricle. Although the ventricle was small in size and thickness, the myocardial fibers were hypertrophied and showed marked widespread fiber disarray or dysplasia. This very diffuse pattern of fiber disarray and hypertrophy occurs in hypertrophic cardiomyopathy with asymmetric septal hypertrophy.[3–9] It may be limited to the interventricular septum in patients with outflow tract obstruction or, as in our patient, may occur in both the interventricular septum and in the free wall in patients with nonobstructive hypertrophic cardiomyopathy.[5] Because the ventricles of our patient were small and not thickened we do not believe that this case represents a hypertrophic cardiomyopathy. Similar fiber disarray also occurs in the ventricle proximal to congenital semilunar valve stenosis with intact ventricular septum,[6,9] but perhaps less extensively than in our patient or in patients with hypertrophic cardiomyopathy.[7,8] This abnormal arrangement of the ventricular fibers may occur as a response to abnormal isometric cardiac contraction.[6] The marked degree of fiber disarray in our patient was probably congenital, perhaps augmented by abnormal regional wall stress.

We believe that this case represents a very unusual congenital biventricular hypoplasia with fiber hypertrophy and disarray that resulted in restrictive physiology, severe A-V valve regurgitation, systemic venous congestion and impaired cardiac output.

Acknowledgment

We are grateful to Robert E. Gulde, MD, for referring this patient.

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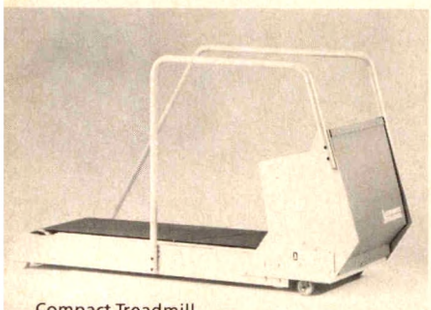
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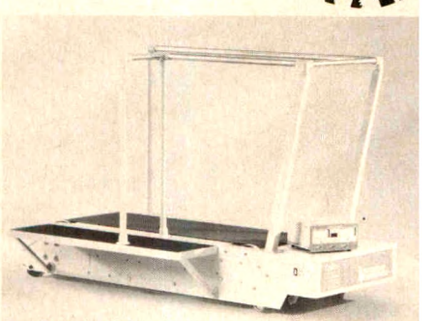
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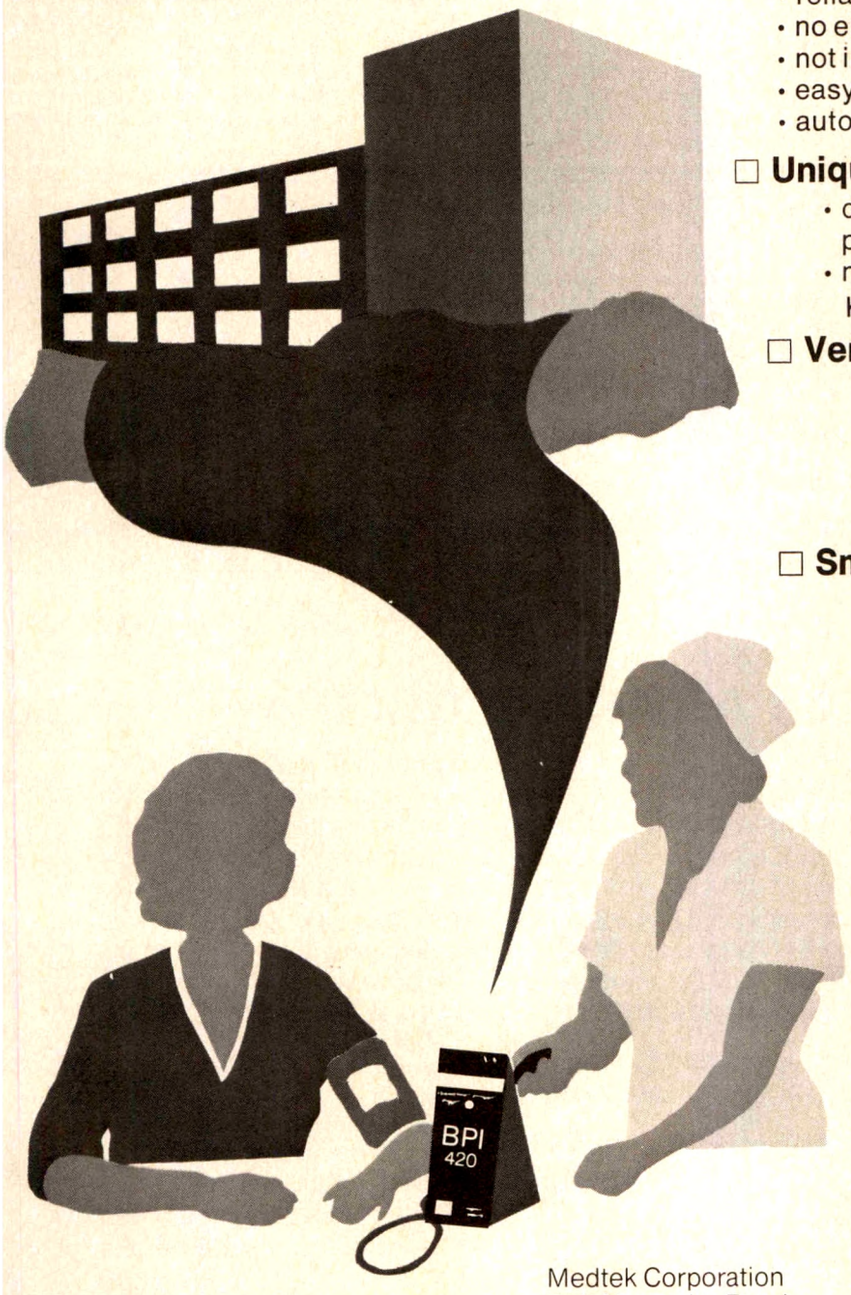
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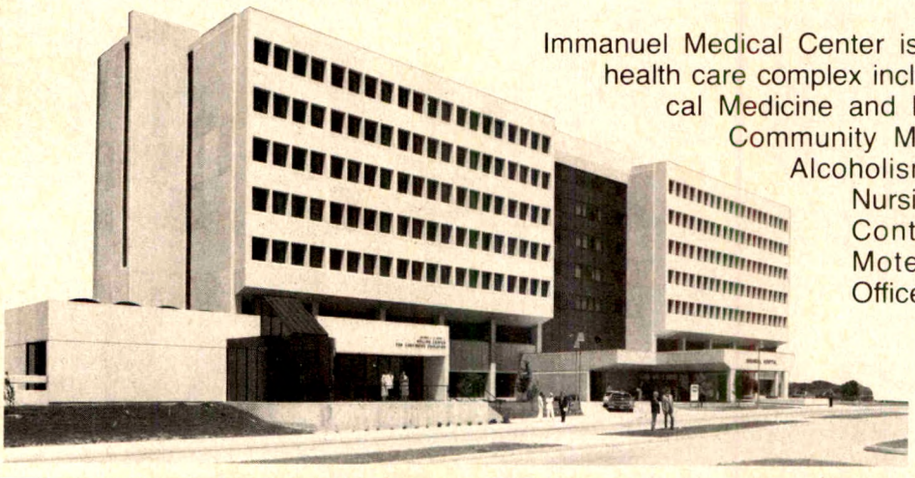
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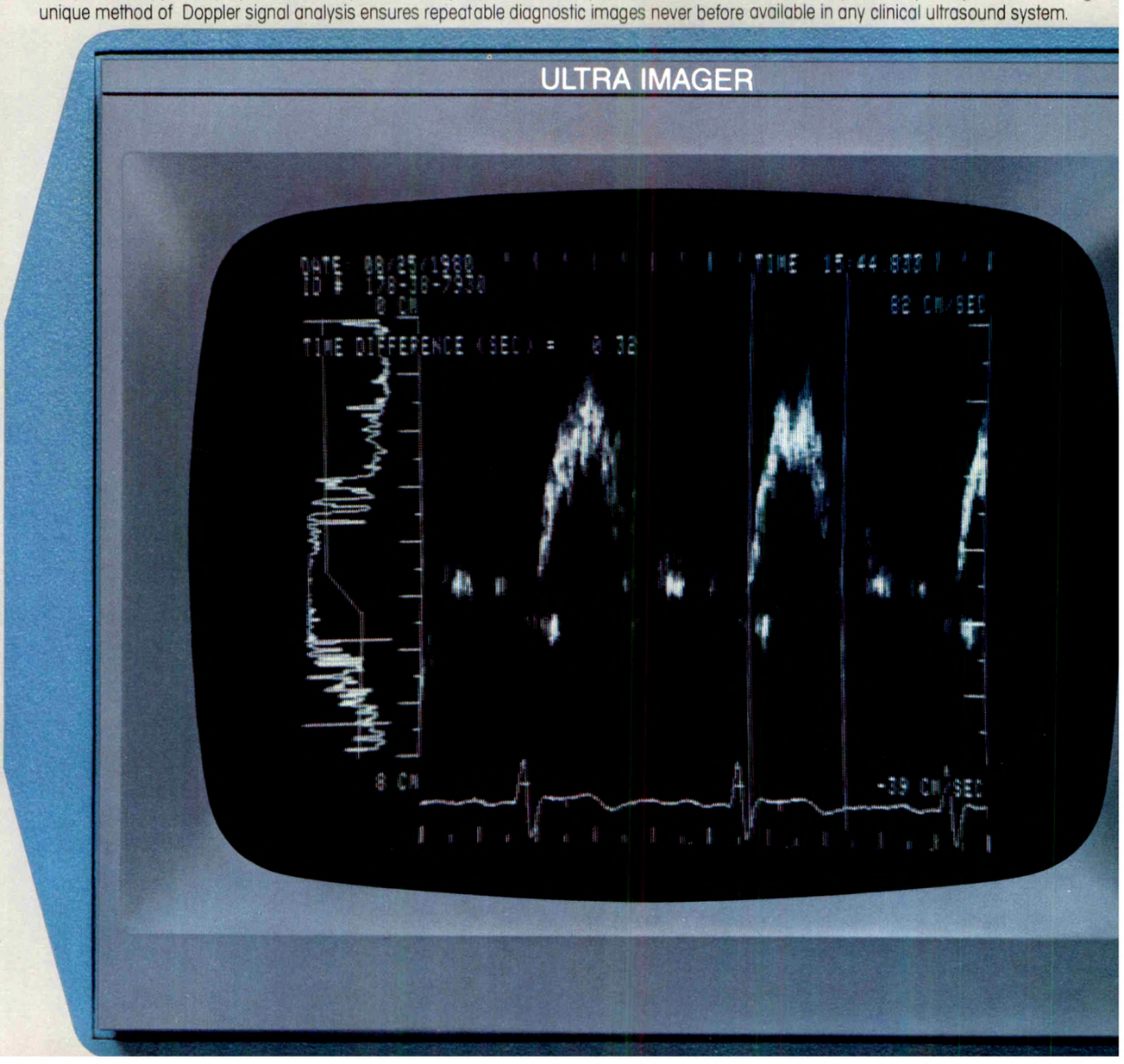
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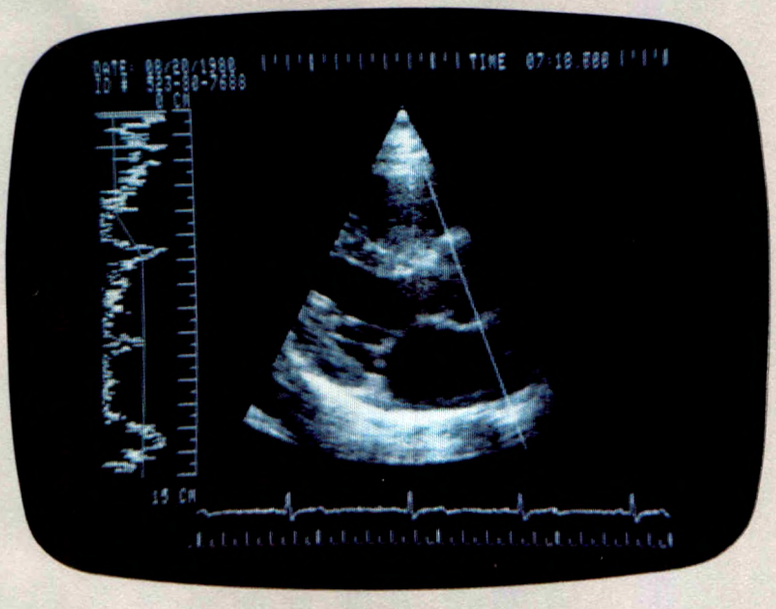
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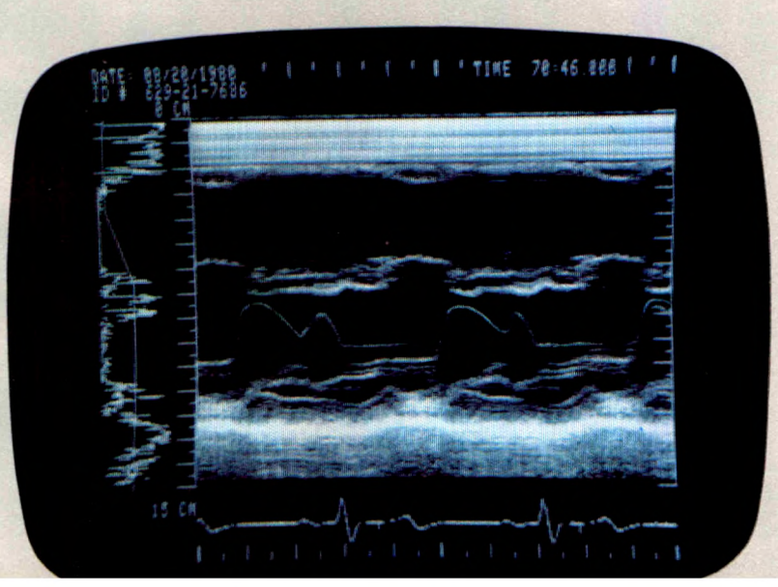
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This pulsed Doppler display is a precise, quantitative representation of a spectrum of blood velocities in the pulmonary artery. The Ultra Imager's unique method of Doppler signal analysis ensures repeatable diagnostic images never before available in any clinical ultrasound system.



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Three complementary imaging modalities:

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On a single video display, the Ultra Imager presents enhanced 2D sector scans, M-mode images or pulsed Doppler data. These three imaging modalities are combined in ways that yield more diagnostic information than ever before. For example, you can change instantly from one mode to another by pressing a button—or use a cursor on a 2D image to determine the placement of an M-mode recording.

The Ultra Imager's multiprocessor system puts cursors and image controls at your fingertips. It also places graphics and alphanumeric messages on the screen to make every examination faster and easier.

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Cost-effectiveness built into the Ultra Imager System

The Ultra Imager offers many cost-effective features that enhance its value to cardiology practice. The mechanical sector scan was selected for the system because it offers superior performance in 2D/Doppler imaging at lower cost. In addition, it will permit ready adaptation to future transducer technologies.

Ease of maintenance is again achieved, along with greater electronic stability, by comprehensive digital processing throughout the system. Integrated design of the Ultra Imager avoids the cabling connections and duplicated components associated with the "stacked box" approach.

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The unique Auto-Test feature of the Ultra Imager allows the system to test itself for failures. If a failure exists, an appropriate indicator light signals the source of the failure. This simplifies servicing of the instrument.

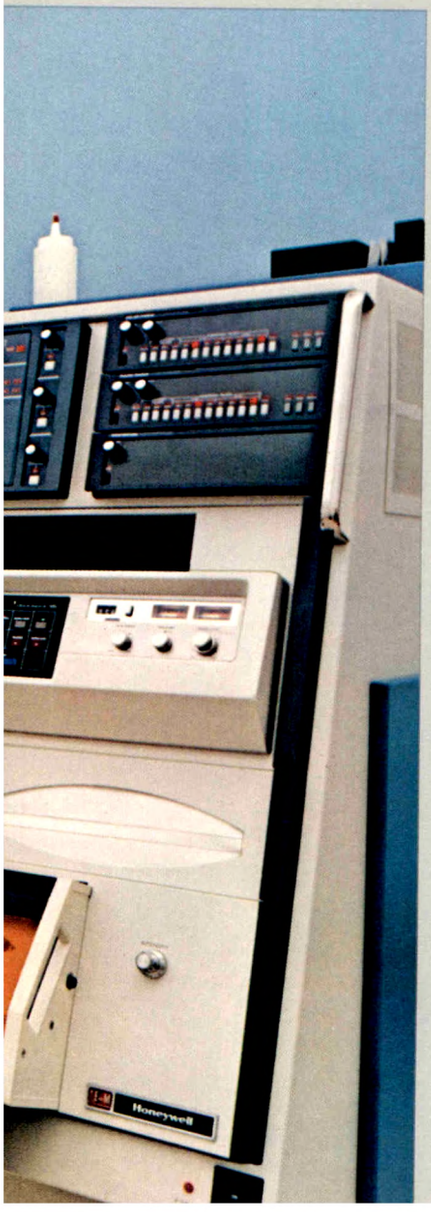
Human engineered with unique operator convenience features

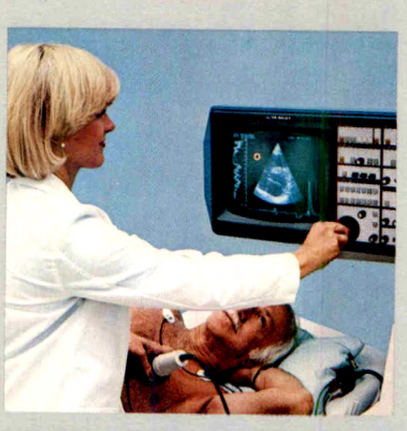
Through careful attention to human engineering details, we have made a sophisticated imaging system easy to operate.

For instance, both the monitor and primary control panel are on a movable gantry that can be positioned near the patient for ease of use and viewing. This makes system controls conveniently accessible to the operator while at the patient's bedside.

The Ultra Imager also includes an audiovisual self-teaching feature which employs the system's videotape recorder to play training programs produced by E for M/ Honeywell. This convenient feature makes staff training a much simpler procedure.

For operator convenience, all displays can be viewed easily even in a daylit room. There is also built-in storage space for gels, tissues, paper and other supplies. Because the cart is compact and easily maneuvered, it can be moved wherever needed.





Operator can position the transducer and be within convenient reach of all necessary scan controls.



Cardiologist can perform off-line data analysis while listening to voice annotations recorded by the operator.



Audiovisual self-teaching feature facilitates training of new personnel.

A versatile imaging system that offers more diagnostic information and greater clinical utility.

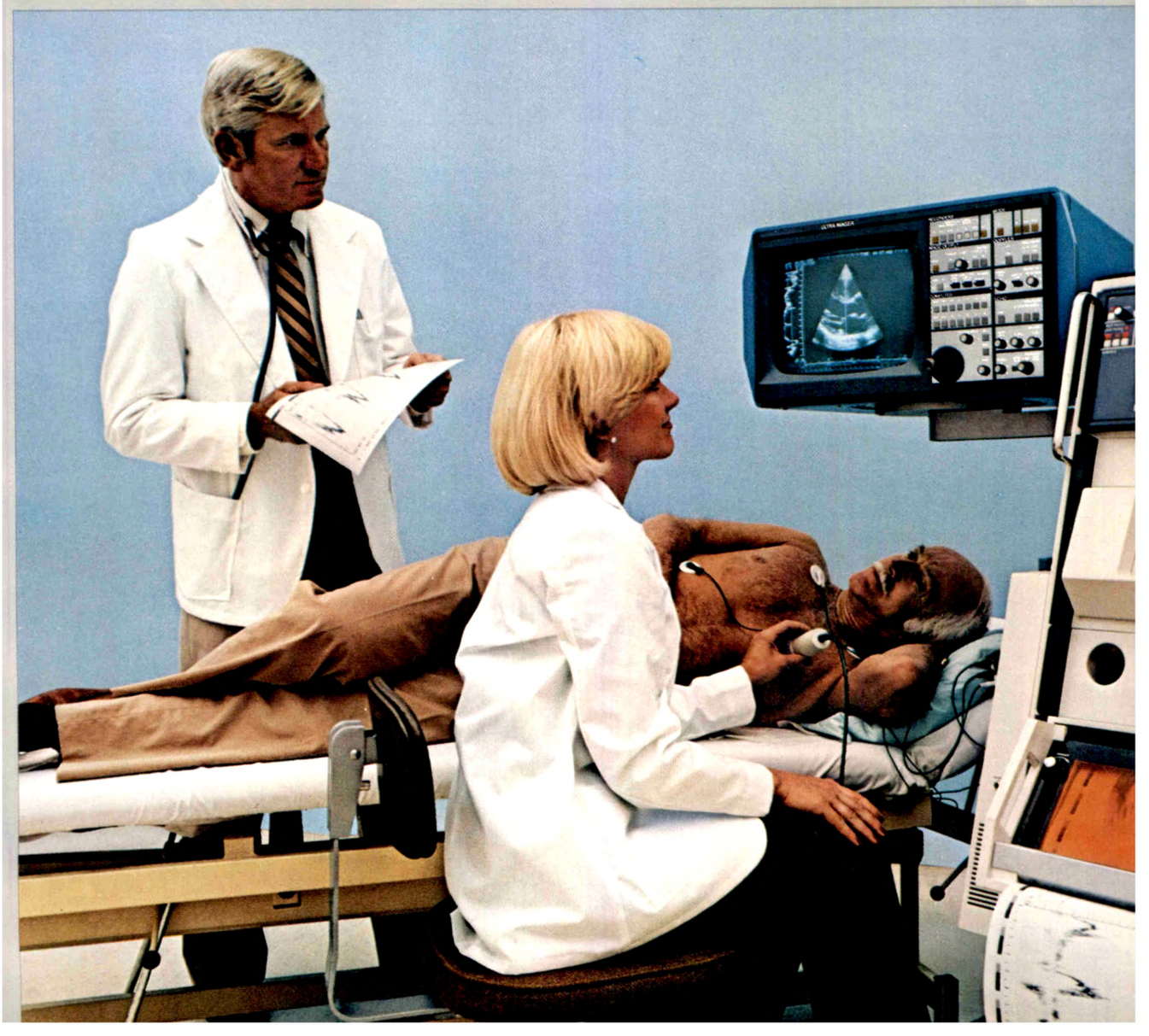
Today the key to diagnostic value in an echocardiography system is the availability of accurate and repeatable pulsed Doppler images. The Ultra Imager offers you this plus the complementary imaging capabilities you need to perform cardiac examinations.

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Honeywell's new LS-8 recorder is a standard system feature. It allows you to make a hard copy of the display with full gray scale reproduction and high resolution. You can select page print or strip chart modes and get crisp, black-on-white records with immediate dry processing.

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E for M/Honeywell has a special commitment to cardiology. Because we've worked with you for over 30 years, we know the kind of service and performance you demand from a medical instrument company. Over the years, we've developed a professional rapport which has led to the development and manufacture of many of the best-engineered, high performance instruments in the healthcare field. The Ultra Imager is one more example of this continuing commitment to excellence.

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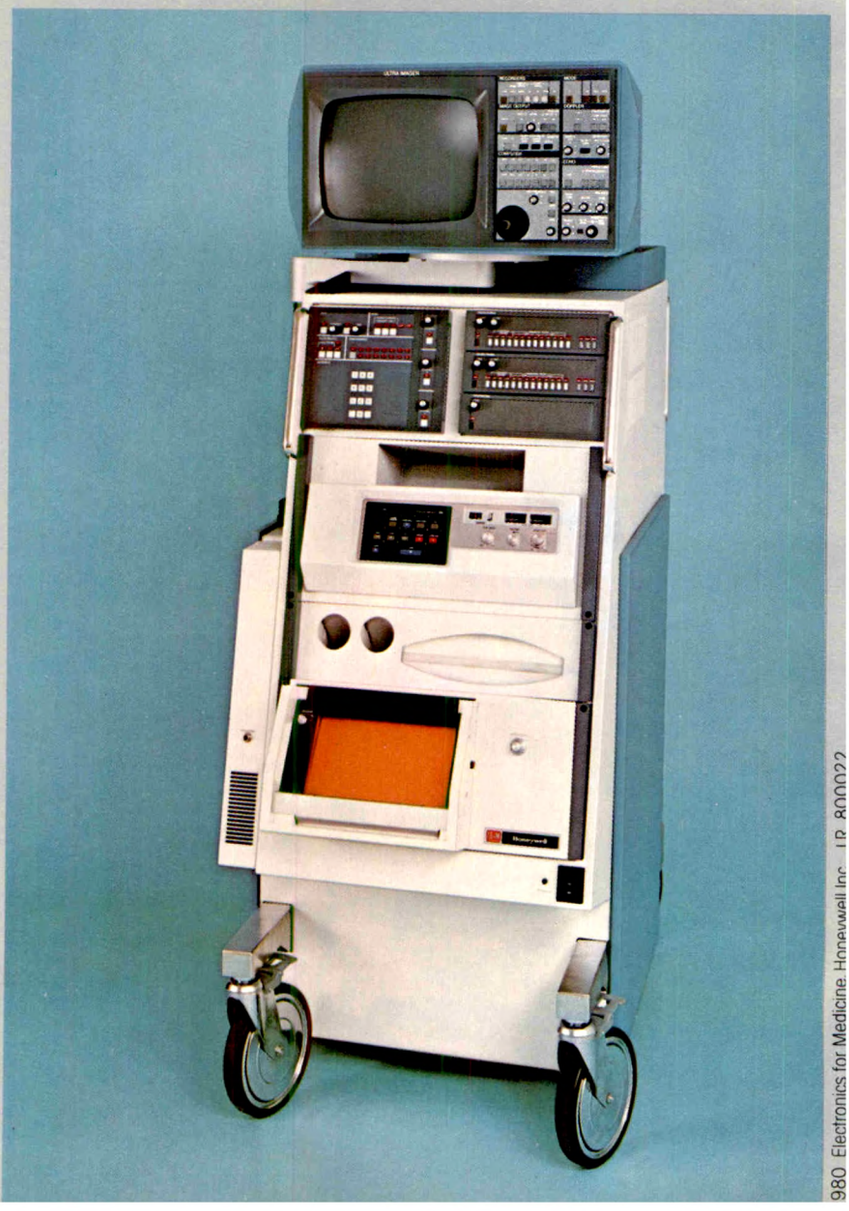
The Ultra Imager's Auto-Test feature further minimizes downtime by pinpointing any failures in the system. Now if a service call is needed the technician knows which parts are required to repair the system on-site. In addition, the Repair/Exchange program provides immediate replacement parts for your service technician with the lowest possible board repair cost through the use of Automatic Test Equipment at the factory.

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LETTERS TO THE EDITOR

NIFEDIPINE IN STABLE ANGINA

In the symposium on nifedipine[1] the efficacy of this drug in the management of Prinzmetal's variant angina was confirmed. However, some questions were raised concerning (1) the role of nifedipine in the treatment of stable angina; (2) potential deleterious effects of use of the drug in association with beta adrenergic blocking agents; and (3) potential negative inotropic effects of the drug. We think that some of these issues have already been sufficiently clarified in several European and Japanese studies:

1. The beneficial effect of nifedipine in stable angina was established in at least six controlled clinical studies[2–7] and was not confirmed in only one study,[8] undertaken in a small group of patients.

2. It was demonstrated[9–11] that the combined use of nifedipine and beta blocking agents decreased the number of anginal attacks and consumption of nitroglycerin. Furthermore, controlled acute studies with bicycle exercise testing[12] confirmed that the combined use of nifedipine and the beta blocking agent oxprenolol produced a greater increase in effort tolerance than did treatment with a single agent.

3. Finally, a negative inotropic effect of the drug was shown only after intracoronary injection in patients with coronary artery disease.[13] In contrast, nifedipine in doses of 10 or 20 mg orally induces a remarkable reduction in peripheral vascular resistance and an improvement in left ventricular performance.[14–16] This favorable effect has been achieved not only in well compensated hearts[14] but also in those with reduced functional reserve. Nifedipine has relieved acute pulmonary edema[15] and improved hemodynamics in patients with chronic heart failure due to congestive cardiomyopathy.[16]

No conclusion can be drawn from these data about the effects of the drug on "contractility"; however, they strongly suggest that the beneficial hemodynamic effects (primarily mediated by the reduction in systemic vascular resistance) overcome the potential negative action of nifedipine, at least at the doses recommended by the manufacturer for oral administration. Further studies should determine whether the hemodynamic changes observed during acute studies persist during long-term treatment and if any untoward effect appears with doses larger than those currently used in the treatment of angina pectoris.

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CORONARY SPASM AND THYROTOXICOSIS

Wei et al.[1] suggested that theirs was the first case showing an association between thyrotoxicosis and Prinzmetal's angina. However, in 1942, Duchosal and Henny[2] described what was possibly the first reported case of Prinzmetal's angina, long before Prinzmetal's classic description. In Duchosal's case there was obvious intermittent S-T elevation associated with pain and the patient was thyrotoxic as judged by the presence of exophthalmus and a goiter.

Of great importance was the statement made by Duchosal and Henny that: "Our observations show that characteristic angina pectoris, responding in a typical way to nitroglycerin, can be produced in the absence of any arterial or arteriolar lesion. The causal role, whether direct or indirect, of a vascular factor cannot be denied as well as a positive action of trinitrin." The characteristic change on the electrocardiogram was a major but temporary increase of the S-T segment. This change could occur in the absence of chest pain and was sometimes precipitated by exercise.

Their patient died 3 days after a thyroidectomy, and postmortem examination confirmed that the coronary arteries were normal. However, the myocardium exhibited a number of degenerative changes, suggesting that repetitive episodes of spasm had caused myocardial damage. It therefore appears that Duchosal and Henny drew, possibly for the first time, attention to the phenomenon of electrocardiographic S-T elevation during anginal attacks in the absence of coronary artery disease.

No doubt other interesting observations were made before those of Prinzmetal and we invite readers who know of such case reports to correspond with us.

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during thyrotoxicosis: response to attaining euthyroid state. Am J Cardiol 1979;43: 335–9.
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REPLY

At the time we submitted our case report we were not aware of the paper by Duchosal and Henny that appeared in 1942. Professor J. P. Delahaye of Lyon, France had also called our attention to this interesting case description. We were also remiss in failing to acknowledge the case reported by Oliva et al.[1] in 1973. Angiographic evidence of reversible spasm in the right coronary artery, associated with chest pain and S-T elevation in inferior electrocardiographic leads, was documented in their patient. Although the patient was euthyroid clinically, thyroid function tests were above the normal range and she was treated with propylthiouracil. Oliva has subsequently informed us (personal communication) that the patient was treated with radioactive iodine for T-3 thyrotoxicosis and has not had an attack of Prinzmetal's angina in 7 years. Our patient remains asymptomatic after $3\frac{1}{2}$ years follow-up.

We have subsequently seen two additional patients in whom the association of hyperthyroidism and coronary arterial spasm appeared to be well substantiated. One of these patients was taking exogenous thyroid medication for a long previously diagnosed hypothyroid condition. She was taking excessive amounts of thyroid because she liked to "run myself a little hyper." Coronary angiography revealed only trivial atherosclerotic disease and after being prevailed upon to reduce the amount of thyroid medication she has remained free of anginal symptoms. We suspect that hyperthyroidism is but one of a number of specific etiologies for coronary arterial spasm. Scleroderma with peripheral and presumably cardiac Raynaud's phenomenon is another that has already been described.[2] This is an area that is ripe for further investigation and we wholeheartedly support the invitation to your readers to report potential associations between coronary spasm and other disease states.

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TREATMENT OF HYPERTENSION AFTER MYOCARDIAL INFARCTION

The paper of Kannel et al.[1] on blood pressure and survival after myocardial infarction shows that patients who were hypertensive before the infarction had a risk of mortality three times greater and patients who were still hypertensive after a coronary event had a risk five times greater than that of comparable normotensive subjects. Further, subjects who had hypertension after angina had become clinically manifest had four times the mortality of those who were normotensive. Patients were examined on the average 1 year after infarction and had biennial follow-up examinations for almost 2 decades. They were considered to be hypertensive when two blood pressure determinations on examination exceeded 160/95 mm Hg. The authors state, "There are many reasons why high pressure should be associated with a poor prognosis after a myocardial infarction. Blood pressure would continue to accelerate . . . coronary atherogenesis and place an increased workload on a myocardium . . . "

We certainly agree with this concept and wonder whether attending physicians attempted to improve the poor prognosis in their patients by lowering arterial pressure. No statement can be found regarding the availability of antihypertensive treatment. However, if these patients were treated, the results of the study cannot be interpreted without information on specific antihypertensive medications in the 22 patients who remained hypertensive after their myocardial infarction. How many were receiving beta adrenoreceptor blocking therapy, which may have a cardioprotective effect, especially after acute myocardial infarction? How many were receiving thiazide diuretic agents with their attendant risks of hypokalemia and (particularly if combined with digoxin therapy) serious arrhythmias? Furthermore, how many of the 32 whose blood pressure reverted to normal or to borderline levels were receiving antihypertensive therapy at the time of their reclassification? We strongly believe that the real value of studies such as this can emerge only in the context of antihypertensive therapy and the effect of this therapy on blood pressure control both before and after myocardial infarction. If, on the other hand, the authors chose not to treat their patients (and we consider that an arterial pressure exceeding 160/95 mm Hg in a patient after a myocardial infarction represents an absolute indication for medical intervention), then they should state why they elected not to do so. Clearly, the patients' compliance seemed not to be a problem because less than 2 percent of the cohort was lost to follow-up. We would greatly appreciate it if the authors could shed some light on these puzzling questions.

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Reference

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REPLY

The Framingham Study has for 3 decades been following up a cohort to determine which factors influence prognosis in cardiovascular disease. All findings uncovered in the course of routine biennial examinations, including blood pressure determinations, are reported to the patient's private physician so that he may take appropriate action. Any abnormal findings are also brought to the attention of the patients by advising them to consult their physician or to continue under his care. We have not dictated to the physician how he should treat his patient.

In Framingham, as elsewhere in the United States, there was a time when hypertension was grossly undertreated. There was also a time (the early 1950s) when no effective

treatment was available. The data referred to span this period. Of the 22 patients who remained hypertensive after infarction, few, if any, were receiving beta blocking therapy because these agents were either not available or not approved for use when the infarcts occurred. A few patients were receiving thiazide diuretic drugs. A decrease in blood pressure was associated with an ominous prognosis even when patients receiving antihypertensive medication were excluded.

We agree that the ultimate test of the efficacy of antihypertensive therapy after an acute myocardial infarction requires a controlled trial. We have attempted only to delineate the natural history in a free-living cohort, relating pressure and change in pressure to prognosis. In particular, we were curious about why data relating hypertension to the first occurrence of myocardial infarction were so clear whereas data relating blood pressure *after* infarction to recurrence of infarction with death were so inconsistent. On the basis of data existing up to that point, we don't see how Messerli et al. could have concluded that arterial pressure exceeding 160/95 mm Hg in a patient after infarction represents an absolute indication for medical intervention. Our data now support this contention, but only a controlled trial can actually prove the point.

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MORTALITY AFTER INFERIOR AND ANTERIOR MYOCARDIAL INFARCTION

In view of the importance of the observations made in the Framingham Study may I draw your attention to an error in the calculation of the expected numbers of deaths in Table III of the paper by Kannel et al.[1] The figures for anterior and inferior infarction should be 18.9 and 23.1, respectively, instead of 16.9 and 25.1. Recalculation of the data shows that the 5 year mortality after anterior infarction is not statistically significantly different from that after inferior infarction.

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Reference

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REPLY

In Table III our calculation of expected deaths is based on age-specific mortality in the groups with anterior and inferior infarction. The expected number of deaths as calculated by Bourdillon is valid only if the age distribution is the same for anterior and inferior infarction. The table could be clarified by adding the following footnote: Expected deaths are age-adjusted.

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BIOCHEMICAL ASPECTS OF ARRHYTHMOGENESIS AND VENTRICULAR FIBRILLATION

The pathogenesis of sudden death and ventricular fibrillation in ischemic heart disease remains hypothetical. Opie and coworkers[1] recently provided critical evidence regarding the understanding of this problem. Animal studies suggest that impaired coronary arterial flow and reperfusion are the basis for the ventricular fibrillation resulting from myocardial electrical alterations consequent to enhanced activity of the sympathetic nervous system and washout products of cell ischemia.[2] We agree that many studies are available on the possible electrophysiologic mechanisms[1] underlying ventricular fibrillation and that biochemical factors—in particular, the relation of magnesium to sudden death in ischemic heart disease—have not been given due consideration.

The metabolic and biochemical changes occurring within seconds and minutes of coronary occlusion or acute myocardial infarction may be related to catecholamines, potassium, magnesium and other washout products of cell ischemia. Thus, it would be valuable to know the magnesium interrelations in various cardiac conditions.

Magnesium excess causes hypotension, bradycardia and conduction defects, whereas in hypomagnesemic patients the electrocardiogram shows S-T depression, T wave inversion and shortening of the P-R interval.[4] Cardiac arrhythmias[4,5] and an increased incidence of digoxin intoxication have also been observed in patients with magnesium deficiency.[6,7] Reports on magnesium ion in relation to ischemic heart disease showed that this ion plays a protective role against death from heart attack in hard water areas.[8] Similarly, cardiac magnesium levels have been found to be decreased in animals[9] as well as in human beings after myocardial infarction[10] and sudden coronary death.[11] Experimental evidence suggests that magnesium deficiency may be associated with hemorrhage, inflammation, degeneration, fibrosis and calcification in the myocardium.[4]

It is apparent from the study of Opie et al.[1] that the electrical effects of increased extracellular potassium are most significant in the pathogenesis of ventricular fibrillation and sudden death due to ischemic heart disease. Other factors such as increased tissue and coronary venous lactate, partial pressure of tissue carbon dioxide and cyclic adenosine monophosphate and severe tissue acidosis help either directly or by causing potassium movements across the cell. We consider that intracellular and extracellular concentrations of magnesium are equally important in changing the electrical activity of the myocardium resulting in ventricular fibrillation and sudden cardiac death.

It has been shown that drug-induced myocardial necrosis and hypoxia-induced electrocardiographic changes can be prevented by prophylactic use of magnesium salts.[12] Thus, it appears to be high time to establish the role of myocardial hypomagnesemia in the genesis of ventricular fibrillation in sudden coronary death. Although many reports on this subject are available,[3,12] further confirmation is needed to determine

whether phophylactic use of magnesium salts will prevent sudden death in ischemic heart disease.

Opie et al. state that clinical use of verapamil is established in the treatment of supraventricular but not of ventricular arrhythmias. Our experience is different and we have successfully treated a large number of patients with ischemic heart disease and ventricular premature complexes with verapamil. In addition, there is some evidence[13,14] to suggest that verapamil has been successfully used in the management of ventricular tachyarrhythmias. This emphasizes the complex behavior of the myocardium in ischemic heart disease in human beings as compared with that in experimental animals.

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REPLY

It may well be that magnesium deficiency is probably underrecognized in patients with chronic cardiac failure on chronic diuretic treatment,[1] and that some could benefit by magnesium replacement. However, a major difficulty with the "magnesium hypothesis" is that there appear to be no data firmly to support the concept that the intra- to extracellular concentration of magnesium is as important as that of potassium in changing the electrical properties of the myocardium. The reported degree of magnesium deficiency in patients with sudden death from heart disease is rather small and is difficult to interpret in the absence of data on the extracellular magnesium concentration in similar circumstances.

That magnesium might play a role in controlling the electrical activity in the heart is suggested by an important paper by Späh and Fleckenstein.[2] They describe a new, preferentially Mg^{++}-carrying transport system working in addition to the fast sodium and slow calcium channels. As antiarrhythmic agents are now being classified to emphasize their activity against either the fast predominantly sodium or the slow predominantly calcium channel,[3] the existence of this new magnesium-carrying channel poses the possibility of a new class of antiarrhythmic agent and allows for a possible role for magnesium in cardiac arrhythmias.

Nevertheless, the hard data linking changes in magnesium ion concentration, whether they be intra- or extracellular, to ventricular fibrillation, are missing and hence were not referred to in our review. Nor did our review attempt to cover the complex matter of digitalis-induced arrhythmias, in which magnesium sulfate might have therapeutic benefit according to animal data.[4]

Verapamil is still generally held by many experienced clinicians not to be very effective in the treatment of ventricular arrhythmias (see Singh et al.)[3].

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RECIPROCATING TACHYCARDIA

Farré et al.[1] described three cases of reentrant tachycardia characterized by an accessory pathway with a very long conduction time incorporated in the tachycardia circuit. Similar cases were reported in 1977 by Coumel et al.[2] and in 1978 by Gallagher and Sealy.[3] In 1976 we[4] reported the results of an electrophysiologic study in a 22 year old patient with an incessant atrioventricular (A-V) junctional reciprocating tachycardia[2] with a rate of about 110/min. Similar to the findings in two patients described by Farré et al.[1] in our patient the P-R interval was longer than the R-P interval. There was also a retrograde sequence of atrial activation. Stimuli delivered in the right ventricle were conducted to the atrium even during A-V nodal refractoriness, thus providing evidence for an accessory pathway as the retrograde limb of the reentrant circuit. The exact location of this accessory pathway could not be identified. This particular form of reciprocating tachycardia seems to be more frequent than previously thought or reported.

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REPLY

Indeed, Pop and his colleagues have described a patient with

slow retrograde conduction of the accessory pathway. Our apologies for not citing their report.

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VERAPAMIL IN ARRHYTHMIAS IN HYPERTROPHIC CARDIOMYOPATHY

Mekenna et al.[1] conclude that alternative antiarrhythmic agents should be sought for the treatment of arrhythmias in hypertrophic cardiomyopathy. They further state that treatment with beta adrenergic blocking agents had no effect on the frequency of serious arrhythmias.

Dhalla[2] suggested in 1976 that myocardial calcium overload may account for some of the cardiac arrhythmias in hypertrophic cardiomyopathy that may lead to sudden death. In that year Kaltenbach et al.[3] reported that verapamil was beneficial in hypertrophic cardiomyopathy. Goodwin and Krikler[4] hypothesized that arrhythmia was the cause of sudden death in hypertrophic cardiomyopathy and proposed that verapamil may be beneficial in patients with hypertrophic cardiomyopathy by inhibiting inward calcium transport through the so-called slow channel, because an increase in myocardial cell calcium content increases myocardial contractility.[5] Therefore, any drug that decreases myocardial contractility should diminish the degree of left ventricular outflow obstruction in patients with hypertrophic cardiomyopathy.

This hypothesis was recently confirmed by Rosing et al.,[6,7] who studied the hemodynamic effects of intravenous verapamil administration in 27 patients with hypertrophic cardiomyopathy. They found that verapamil can significantly decrease left ventricular outflow obstruction and improve exercise capacity and symptomatic status in patients with hypertrophic cardiomyopathy.[6,7] Furthermore, verapamil has been demonstrated to decrease a rapid ventricular rate in patients with atrial fibrillation, even resulting in conversion to sinus rhythm in some cases,[8–12] and proved very effective in the treatment of paroxysmal supraventricular tachycardia.[9,10] Because it selectively inhibits membrane transport of calcium, it also posseses peripheral and coronary vasodilator properties and is thus useful in angina pectoris.[10]

I strongly believe that recent reports attesting to the efficacy of verapamil in the management of patients with hypertrophic cardiomyopathy provide physicians with a new therapeutic agent that has a beneficial effect on left ventricular outflow obstruction, arrhythmias and angina pectoris. Verapamil also has the therapeutic advantage over beta adrenergic blocking drugs in the treatment of patients with chronic obstructive lung disease or diminished myocardial reserve.[12] Its introduction into the United States will constitute a very significant advance in cardiovascular therapeutic armamentarium.

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REPLY

Cranefield et al. demonstrated that many ventricular arrhythmias depend on the fact that the myocardium is partially depolarized; activation from such a level is dependent on the slow calcium channel, and Goodwin and Krikler (Ahmad's Ref 4) suggested that calcium antagonist agents may protect the ventricles against ventricular arrhythmia and fibrillation. However, our studies using verapamil (480 mg/day) in patients with hypertrophic cardiomyopathy and ventricular arrhythmia,[2] show no reduction in the frequency of serious ventricular and supraventricular arrhythmias, and thus we are investigating other agents including amiodarone.

Increasing experience with hypertrophic cardiomyopathy persuades us that important hemodynamic obstruction to left ventricular outflow must be a rare event and that gradients are not an essential feature of the disease, which is mainly notable for the impairment of diastolic function.[3] A left ventricular outflow tract gradient is diagnostically useful because it is usually associated with easily identifiable physical and echocardiographic signs. However, the presence of a gradient is not associated with an increased incidence of angina, dyspnea,[4] serious ventricular arrhythmia[5] or poor prognosis[6] and thus the significance and importance of the reduction in the left ventricular gradient after verapamil demonstrated by Rosing et al. (Ahmed's Ref 6) is uncertain.

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DIASTOLIC ABNORMALITIES OF FLAIL MITRAL LEAFLETS IN THE TWO DIMENSIONAL ECHOCARDIOGRAM

Mintz et al.[1] provide significant and dramatic evidence of the ability of the two dimensional echocardiogram to diagnose flail mitral leaflets. In their study loss of systolic mitral leaflet coaptation was the sole criterion for establishment of the diagnosis. Although this criterion is essentially defining and the most direct, technical problems can occasionally obscure the mitral leaflets during systole during maximal motion of the heart.

We have found that the diastolic appearance of the mitral valve can also provide valuable information. Three patients whose mitral leaflets were obscured in systole were prospectively diagnosed as possessing a flail anterior leaflet because of a commonly shared diastolic appearance. During the minimal flow period of mid diastole, lack of chordal support to the free edge of the mitral anterior leaflet was evidenced by a distinctive "sagging" appearance (Fig. 1). This appearance is not seen in leaflets with normal diastolic chordal support. There is also a characteristic motion of this untethered portion of the leaflet identifying a hinge point between supported and unsupported leaflet segments.

The high diagnostic sensitivity obtained by Mintz et al. in their series may not be attained in all laboratories practicing this technique-dependent procedure. This additional criterion in the less artifact-prone diastolic phase of the cardiac cycle may be helpful.

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Reference

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REPLY

We have seen this "sagging" of the leaflet not only during mid diastole, but also during end-diastole as the mitral leaflet begins to close. The sign does not occur in all patients with flail mitral valve; in particular, we have never seen it in patients with a flail posterior leaflet. Furthermore, if diastasis does not occur (for example, in patients with significant tachycardia), diastolic sagging may not occur. Other causes of mitral insufficiency can give a similar appearance to the anterior mitral leaflet during diastole: endocarditis (with a vegetation, but without flail leaflet), possibly rheumatic mitral valve disease and possibly mitral valve prolapse (because of the thickened leaflet or localized chordal elongation). This interesting observation, like all proposed diagnostic criteria, requires statistical analysis to determine its true significance.

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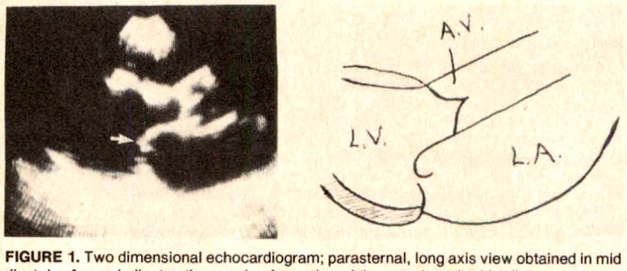


FIGURE 1. Two dimensional echocardiogram; parasternal, long axis view obtained in mid diastole. **Arrow** indicates the sagging free edge of the anterior mitral leaflet.

EFFECT OF HANDGRIP ON SYSTOLIC ANTERIOR MOTION OF THE MITRAL VALVE: AN ECHOCARDIOGRAPHIC FINDING IN HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

To the seven echocardiographic features of hypertrophic cardiomyopathy described by Doi et al.,[1] one should add an eighth: the effect of handgrip on the systolic anterior motion of the mitral valve.

The isometric effort results in an important pressor response with elevation of afterload.[2] This, in turn, causes an attenuation or diminution of the systolic anterior motion in the echocardiogram and a concomitant softening of the accompanying murmur (Fig. 1). A similar maneuver performed during cardiac catheterization results in a reduction of the left ventricular outflow gradient (Fig. 2) and its reappearance almost instantaneously, as the handgrip is released (Fig. 3). The three figures were obtained from three different patients. This response resembles that observed during squatting[3] and is, I believe, an additional important diagnostic sign that is easily elicited and reproduced at the bedside or in the course of invasive cardiac investigation.

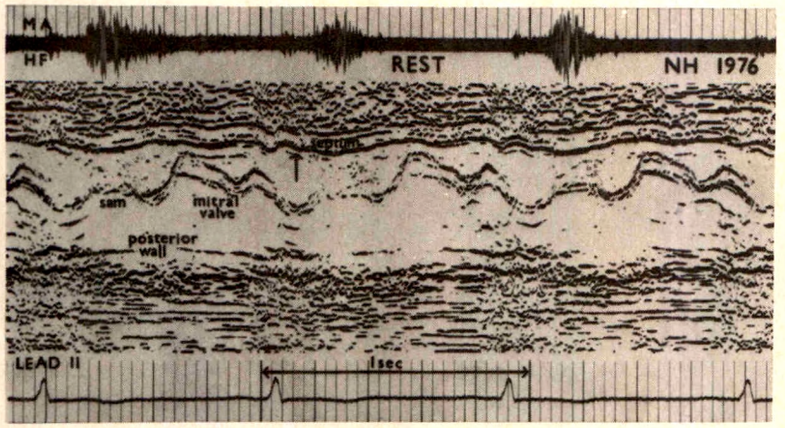
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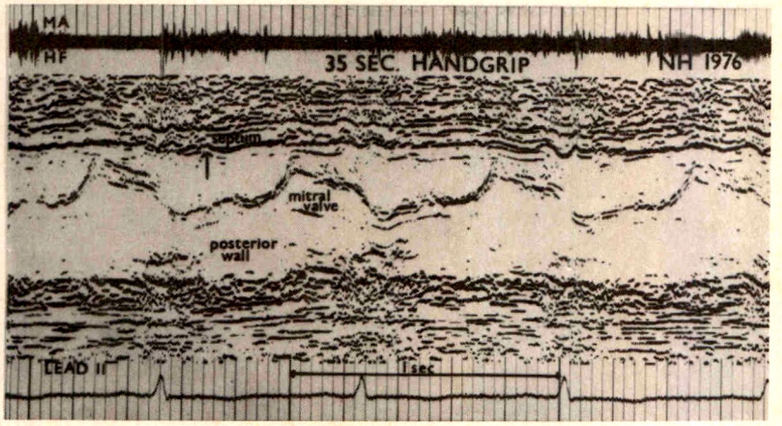
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REPLY

In hypertrophic cardiomyopathy the physiologic response to an increase in afterload induced pharmacologically or by isometric exercise is a decrease in left ventricular outflow gradient, a decrease in the duration and intensity of a systolic murmur and, apparently, a reduction in systolic anterior motion of the mitral valve. Patients who show true systolic anterior motion of the mitral valve usually have classic signs of hypertrophic cardiomyopathy with a left ventricular gradient and do not pose a diagnostic problem. A maneuver that





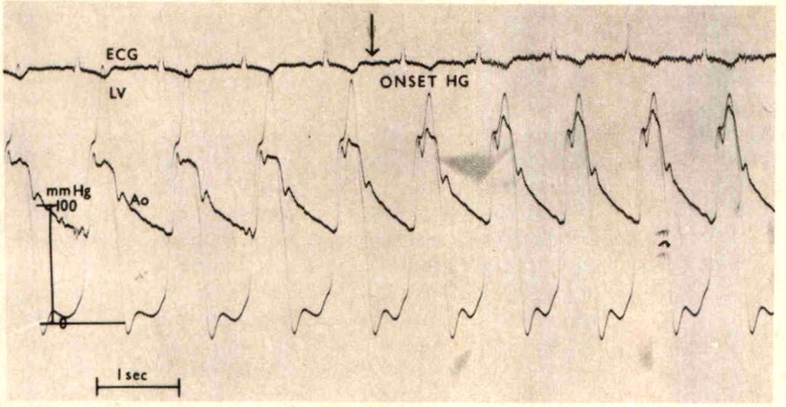
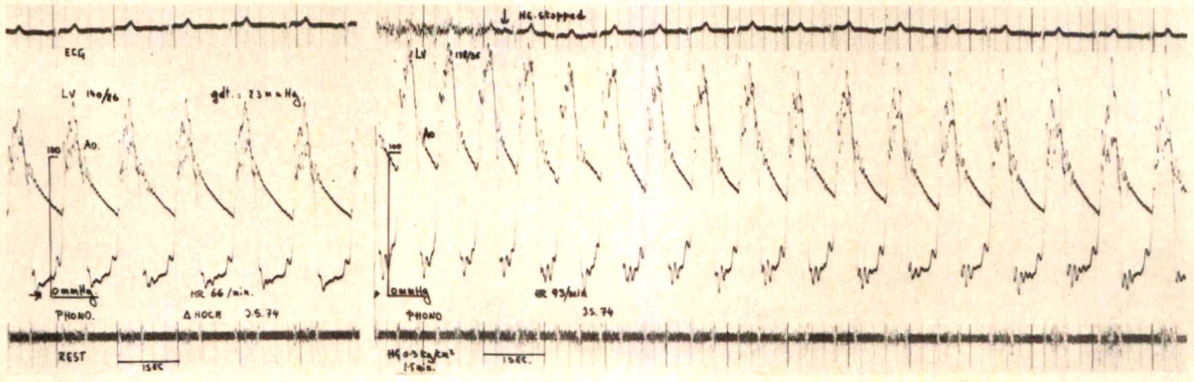


FIGURE 1 (top two panels). Above, the characteristic systolic anterior motion (SAM) with a late systolic murmur. **Below,** after 35 seconds of isometric exercise (0.3 kg/cm^2), the murmur has softened and the systolic anterior motion has been abolished. This also illustrates an increase in left ventricular dimension at end-systole.

FIGURE 2 (panel 3). Pressure tracing. There is a resting gradient between the apex of the left ventricle and root of the ascending aorta. Shortly after the start of handgrip (↓), the aortic pressure increases and the gradient is reduced.

FIGURE 3 (bottom panel). Pressure tracing. **Left,** a small resting gradient is evident. **Right,** at the end of 1.5 minutes of handgrip, there is no gradient. Both left ventricular and aortic pressures have increased. The heart rate has increased from 66 to 93 beats/min. As the handgrip is stopped (↓) there is an immediate reduction in both left ventricular and aortic pressures, and after a few beats the gradient reappears as the murmur increases in intensity.



removes one of the most important of the echo abnormalities in hypertrophic cardiomyopathy would be diagnostically useful only if it made it more specific. Systolic anterior motion of the mitral valve is seen in other conditions, but the response to an induced increase in afterload may be similar to that described in hypertrophic cardiomyopathy.

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FEVER IN AORTIC DISSECTION

Ruderman et al.[1] in their letter emphasize the occurrence and importance of fever as a manifestation of dissecting aneurysm of the aorta. This relation, of course, has been documented previously.[2,3] In the patient presented by Ruderman et al., a history of chest pain and abnormal chest X-ray findings led to cardiac catheterization and aortography. However, even in the absence of pain or an abnormal chest X-ray film, one must still entertain the diagnosis of aortic dissection and maintain a high index of suspicion when fever occurs in association with other manifestations of aortic dissection.

Case report: A 48 year old man had a severe flu-like syndrome and was found to have a loud murmur of aortic incompetence. He was admitted to a referral hospital with a fever of 39.5° C and severe congestive heart failure. There was no history of chest pain. Blood cultures were negative and he was transferred to our institution when congestive heart failure proved refractory to medical therapy. He underwent cardiac catheterization which demonstrated severe aortic insufficiency. A supravalvular aortogram was performed but usual cineangiographic views failed to demonstrate dissection, focusing on the proximal ascending aorta and left ventricle. Seven days after catheterization, blood cultures remained negative. Because of severe congestive failure, the patient underwent operation. At operation, the ascending aorta was found to have dissected, was paper-thin and measured 10 cm in width. The aortic valve was resuspended and the ascending aorta replaced with a 26 mm Dacron® graft. The patient's postoperative course was entirely uncomplicated and he was discharged on the 7th postoperative day with normal hemodynamics and no diastolic murmur.

Comment: In this patient, no chest pain was present and no radiologic abnormalities of dissection were present. An aortogram would have been diagnostic and outlined the anatomic defect. In a patient with negative blood cultures and aortic valve incompetence of recent onset, we believe an aortogram is indicated to evaluate the possibility of aortic dissection. We certainly agree with Ruderman et al. that catheterization should not be delayed by the presence of fever.

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COMPLICATIONS OF INTRAAORTIC BALLOON COUNTERPULSATION

Isner et al.[1] indicate a 36 percent rate of complications related to the use of the intraaortic balloon counterpulsation device in 45 patients studied at necropsy. They further state that the number of complications has been underestimated until now.

The statement may be misleading, in that the authors do not include pertinent data to permit the true incidence of complications to be assessed more accurately. They do not report how the study group was selected from patients who underwent the treatment, the total number of the latter or the number of patients who died but who did not undergo necropsy. No adequate clinical data are included to indicate a cause and effect relation between the complications and the death of the patients in most of the cases. Thus, an unfair opinion may be formed of the complications of the method, which has undoubtedly helped to keep alive patients who probably could not have been salvaged by conventional means only.

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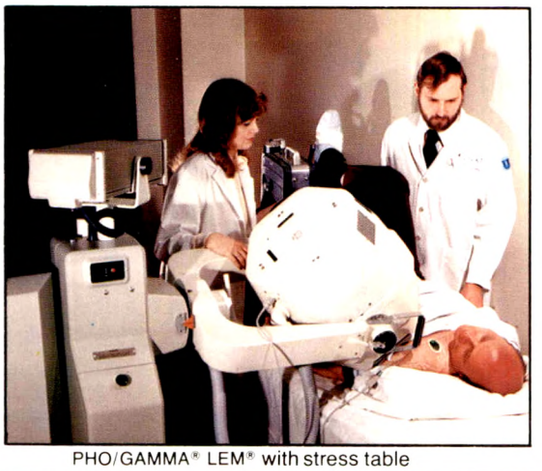
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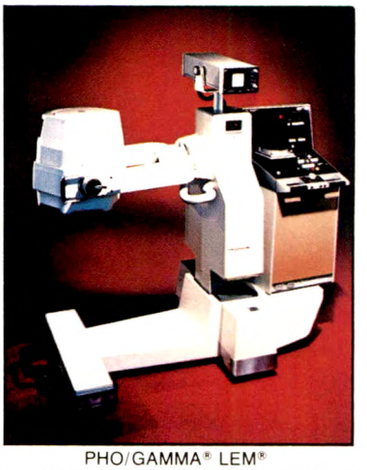
REPLY

Our paper concerned the frequency of complications observed in a necropsy group of patients who had had the intraaortic balloon inserted shortly before death. Among these necropsy patients, the percent who had complications from insertion of the balloon was surprisingly high. We have no information on complications from this device in patients who died but did not undergo autopsy. There are numerous reports describing various frequencies of complications of this device in patients who are alive or have died and no autopsies have been done. Our presentation was not an epidemiologic type or study but simply a study of necropsy patients. The message nevertheless is quite clear: among necropsy patients who have had the intraaortic balloon device inserted shortly before death, the frequency of complications is much higher than that predicted from purely clinical studies. Our study was not an attempt to criticize the intraaortic balloon device but simply to point out that it carries with it a relatively high frequency of complications, some of which are important clinically and some of which are not.

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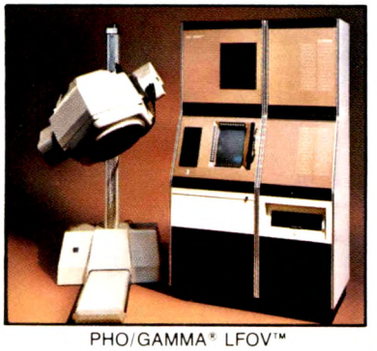
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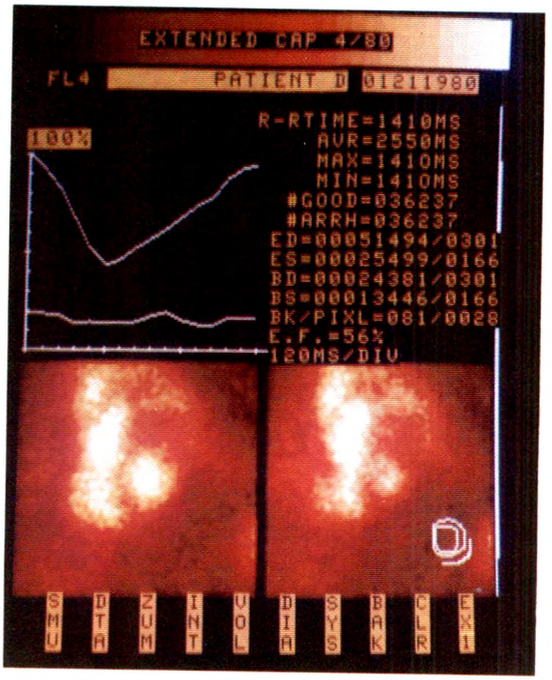
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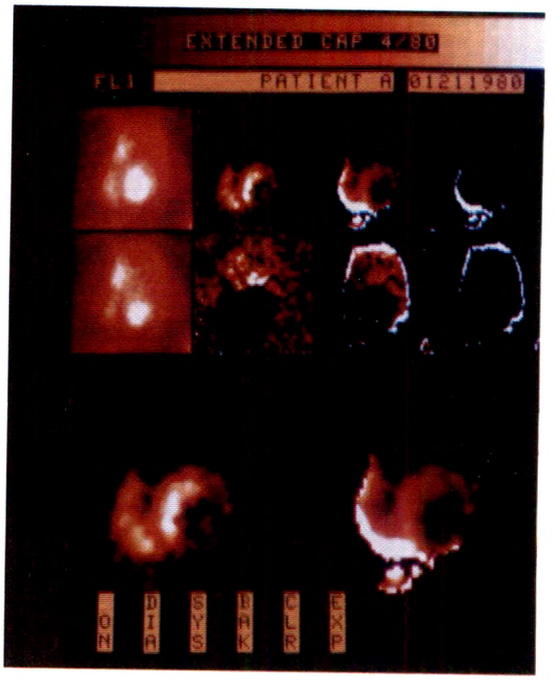
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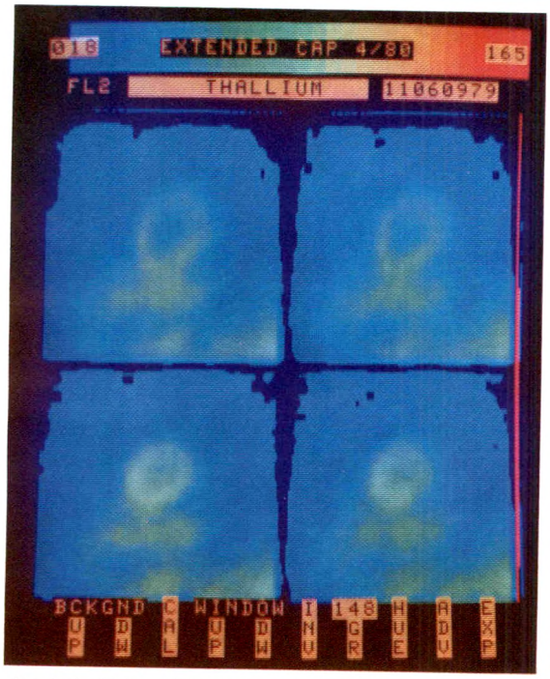
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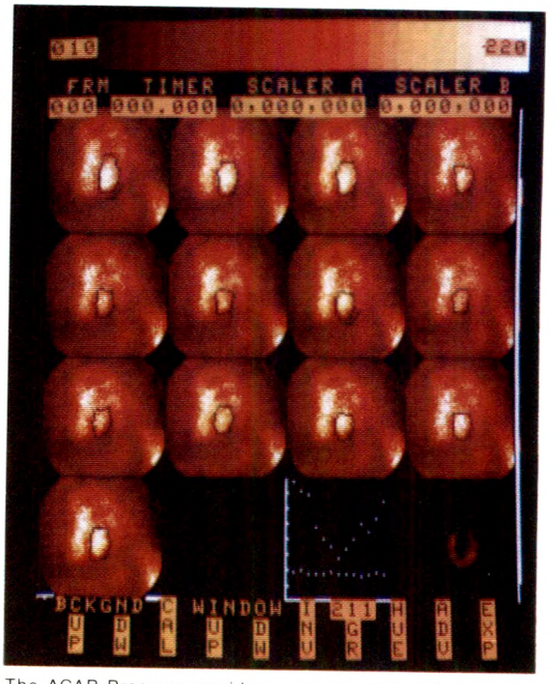


Regional wall motion changes within the heart can be displayed through "stroke volume" and "ejection fraction" images. Additionally paradox images enhance the diagnosis of dyskinetic myocardial segments for complete cardiac analysis.





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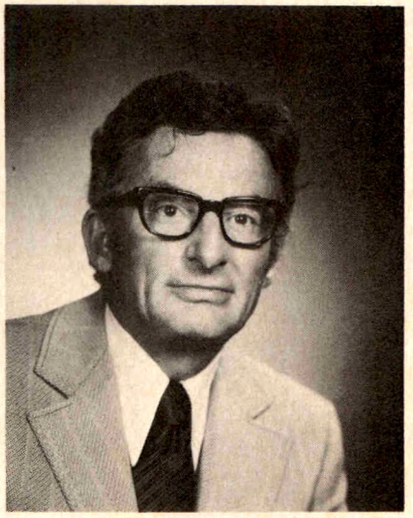
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President's Page: Challenges and Frustrations



Robert O. Brandenburg, MD, FACC

The challenges, stimuli and frustrations involved in the practice of clinical cardiovascular disease undergo continual change. Young cardiologists often receive their main challenge and stimulation from involvement with invasive techniques, such as cardiac catheterization, coronary arteriography, Swan-Ganz and pacemaker procedures. Others find investigation the most satisfying. Another subset find electrocardiography and electrophysiologic studies their main areas of interest. With other groups, it is echocardiography or nuclear imaging procedures. Many of the cardiac consultants involved with invasive procedures phase out of this area by the age of 45 or 50 years or become directors of laboratories of cardiac catheterization (but no longer actually perform the procedures). Interest and involvement in the noninvasive procedures appear to be more lasting.

The useful and important skills related to these procedures may serve to direct interest away from the patient and the disease. The interest on hospital rounds is not in Mrs. Smith and her heart disease, but on the "square root sign in early diastole in the ventricular pressure curve," "premature closure of the aortic valve by echocardiogram," "the drop in ejection fraction with exercise by nuclear imaging," and so forth. The wise, mature and skillful cardiovascular clinician usually (but, unfortunately, often not until mid-life or later) learns to give proper emphasis and de-emphasis to the huge amount of data now potentially available and attainable. The important characteristics of selectivity have become well developed in this clinician. He or she does *not* need an echocardiogram, treadmill test, nuclear studies and cardiac catheterization for every patient with a significant cardiac lesion. Nor is a coronary arteriogram necessary for every patient with chest pain. Like Willie Sutton, this clinician has learned where the "gold" is and only occasionally must tap multiple banks. Many times the gold is at the bedside, related to proper use of ears, hands and eyes. The clinician gains stimulation and is challenged to develop a management scheme for the patient with a thoughtfully chosen, limited number of special studies. The patient's course is likely to be enhanced and much less expensive with this course of action.

The mature clinician also has learned to be wary of the initial claims for new drugs, new operations and procedures until experience and scientific scrutiny have indicated their probable worth. At the University of Pennsylvania Medical School in the 1940s, Dr. Perry Pepper was chairman of the Department of Medicine. Many of us will recall his unique discussion of the "fever curve of new drugs." There would be a rapid upward movement related to the wave of enthusiasm and acceptance—then a downward trend as reports of side effects, serious reactions and, occasionally, death occurred. Finally, after a number of years, the drug would assume its proper role with its benefits, limitations and hazards now established. Dr. Pepper described the ease with which he and his colleagues had been led astray by wishful thinking when testing a new drug designed to lessen the fibrosis and scarring of heart valves from rheumatic fever. He recalled how certain the house staff had been that the murmurs had decreased over a period of time as had the patients' symptoms. Experience, of course, finally disclosed that the drug had no value except for its placebo effect. It has not been heard from again. Prosthetic heart valves have occasionally followed the same course.

The cardiovascular community is now reaping the rewards of the investigations of a few decades ago. As a result, the improvements in understanding, in diagnostic techniques and in methods of treatment have clearly surpassed those of any other subspecialty of medicine. We are indebted to our investigators of a few decades ago and must continue to encourage and promote the development of a continued supply of these creative persons. Unfortunately, the number of cardiovascular investigators who are physicians has been decreasing in recent years. Although basic investigation has resulted in our current level of sophistication in diagnosis and treatment, it has sometimes created a wedge between patient and physician. As consultants and teachers we must make wise and intelligent use of these new tools to avoid both overuse and underuse. Many examples can be given of both. I frequently see young, middle-aged and older patients who have had episodes of paroxysmal atrial fibrillation. (Careful auscultation has excluded mitral valve disease and there is no clinical or laboratory evidence of hyperthyroidism.) Most such episodes have followed periods of unusual fatigue and heavy smoking, or overindulgence in alcohol. Such patients, in addition to the

routine tests, have commonly had an echocardiogram (reasonable, but unnecessary) and a coronary arteriogram, which seems totally inappropriate, adding no information of benefit in the management of the patient. Young women with mitral valve prolapse and various forms of atypical chest pain have been subjected to coronary arteriography to "reassure them about the absence of disease." The study has clearly not reassured many of them, since they continue to go from consultant to consultant seeking an explanation of their problem.

Cardiovascular consultants have occasional reason to feel frustration (inability to make a precise diagnosis, inability to get procedures or laboratory tests done when and as they wish, dealings with the patient "who won't get well," and so forth), but patients also have frustrations that seem warranted. Some of these involve differences of opinion: The cardiologist at home says operation is not indicated; the surgeon says it is urgent (occasionally the roles are reversed). Frequently one encounters the frustrated patient who has symptoms, sometimes with and sometimes without evidence of cardiovascular disease, who has undergone various diagnostic studies. A communication breakdown has occurred so that either the patient was too anxious to hear what was said, or it was said in language unintelligible to the patient, or it was not said (perhaps simply, "Your tests are normal"). The patient's anxieties and many concerns about prognosis, limitations and treatment are unresolved. He complains: "My doctor doesn't tell me anything." In most instances this is an overstatement, but the patient's unhappiness and frustration are evidence we have failed in our mission. If we are to be responsible for the time, expense and occasional risks involved in special studies it should be our responsibility to spend the necessary time to answer and resolve the patient's questions. There sometimes seems an inverse ratio between the special studies and the time spent with the patient. Clearly problems of time are important to all of us, but a little extra time used efficiently will result in more patient satisfaction and less need for patients to utilize the services of multiple consultants.

Robert O. Brandenburg, MD, FACC
President
American College of Cardiology

ANNOUNCEMENT OF 1981 PEDIATRIC CARDIOLOGY EXAMINATION

The Sub-Board of Pediatric Cardiology of the American Board of Pediatrics will offer its next written examination on Friday, July 10, 1981.

The following criteria must be met to qualify to sit for the examination:

1. Certification by the American Board of Pediatrics;
2. Two years of full-time graduate training in an accredited pediatric cardiology program;
3. Letters of recommendation from individuals able to attest to the applicant's fellowship training.

Candidates who achieve a qualifying score on the written examination will be eligible for the oral examination. The oral portion of the examination will be held in October 1981, in New Orleans. A candidate must be successful on both the written and oral portions of the examination in order to be certified.

The registration period for the examination will extend from December 1, 1980 to March 31, 1981. Please contact the American Board of Pediatrics during that time if you wish to receive an application for the examination.

The application fee for the written portion of the examination is $300 ($150 processing, $50 registration, $100 examination fee). An additional fee of $150 will be payable upon receipt of an appointment for the oral examination.

Please direct inquiries to: American Board of Pediatrics
Suite 402, NCNB Plaza
136 East Rosemary Street
Chapel Hill, NC 27514
(919) 929-0461

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the Continuing Education Committee for Extramural Programs assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The Continuing Education Committee for Extramural Programs of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

NOVEMBER 1980 THROUGH MARCH 1981

1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

NOV. 5–7 — **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. The New York Hilton, New York, NY

NOV. 29–DEC. 1 — **Advances in Heart Disease 1981.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 4–6 — **Two-Dimensional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director and Leonard S. Dreifus, FACC and Gerald M. Pohost, FACC, co-directors. The Franklin Plaza Hotel, Philadelphia, PA

DEC. 7–10 — **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multi-Disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 12–14 — **Cardiovascular Disease: Achievements and Challenges 1980.** Henry I. Russek, FACC, director, Sheraton Centre, New York, NY

1981

JAN. 12–16 — **Twelfth Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Opticon Theatre, Snowmass Resort, Snowmass, CO

FEB. 2–4 — **Clinical Echocardiography 1981—M-Mode, 2-Dimensional and Pulsed Doppler Techniques,** Pravin M. Shah, FACC, director and John S. Child, FACC, Joseph K. Perloff, FACC, and Maylene Wong, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

FEB. 9–11 — **Calcium (Slow Channel)-Inhibiting Drugs in Cardiovascular Therapy: Mechanism of Action and Application.** Borys Surawicz, FACC and Attilio Maseri, FACC, directors. New Orleans Marriott, New Orleans, LA

FEB. 19–20 — **Ventricular Arrhythmias and Sudden Cardiac Death.** Thomas B. Graboys, FACC and Bernard Lown, FACC, directors. Sheraton Boston Hotel, Boston, MA

MAR. 30–APR. 3 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Krannert Institute of Cardiology, Indiana University Medical Center, Indianapolis, IN

CARDIOLOGY BOARD REVIEW: Update in Cardiology

September 9–11, 1981 — **Atlanta, Georgia**

Presented by: The American College of Cardiology

***Directors:* J. WILLIS HURST, MD, FACC and ROBERT C. SCHLANT, MD, FACC**

For brochure and further information contact: Registration Secretary, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone: Area Code 301 897-5400

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's Learning Center is located at the College's headquarters in Bethesda, Maryland. The purpose of the Learning Center is to support professional commitment to quality patient care by providing a standard of excellence in continuing medical education.

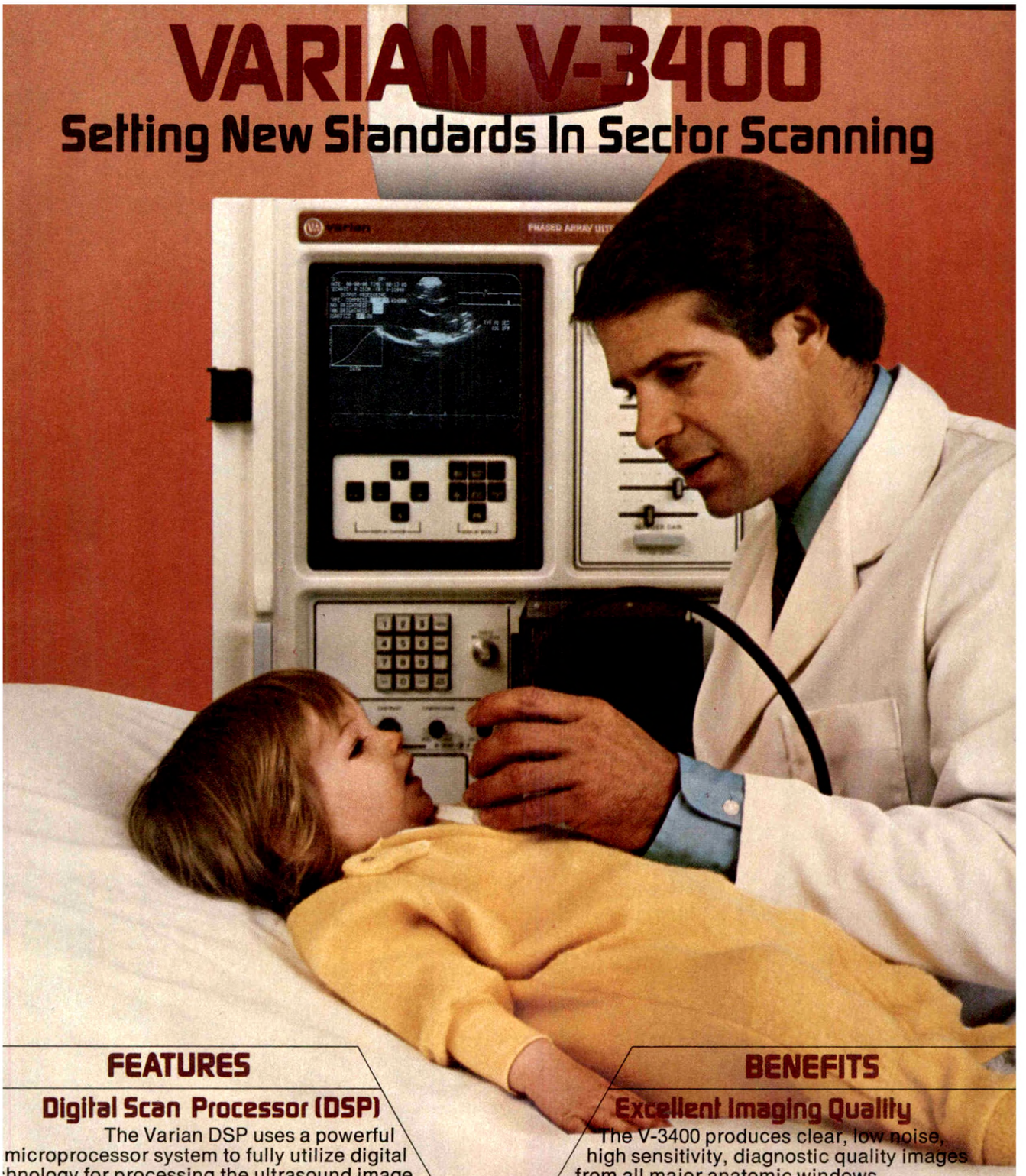
For additional information or a complete program calendar, contact the Program Registrar, Heart House Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

LEARNING CENTER PROGRAMS: JANUARY to JULY, 1981

Program Number	Date	Program Director	Title of Program
308	January 12–13	William Grossman, MD	The Role of the Cardiac Catheter in the Patient with Heart Disease
309	January 15–16	Samuel Kaplan, MD and Winston E. Gaum, MD	Cardiac Electrophysiology and Rhythm Disorders in Pediatrics
334	February 5–6	August M. Watanabe, MD	Myocardial Metabolism and Neurogenic Control of Circulation: Application to Clinical Cardiology
333	February 12–14	H. J. C. Swan, MD	Therapy of Acute Infarction: Afterload Reduction
310	February 16–18	Sylvan Lee Weinberg, MD	Supervisor's Role in Cardiovascular Nursing and Training
311	February 23–25	William C. Roberts, MD	Congenital Heart Disease: The Multidisciplinary Approach
312	March 2–4	Nanette K. Wenger, MD	Rehabilitation of the Cardiac Patient
313	March 30–31	Jere H. Mitchell, MD	Cardiovascular Benefits and Risks of Exercise
314	April 1–3	J. O'Neal Humphries, MD	Coronary Bypass Surgery—Facts and Fancy
315	April 8–10	Victor Parsonnet, MD	Current Concepts in Pacing
316	April 13–15	Keith Cohn, MD	Exercise Testing: Diagnostic and Physiological Considerations
317	April 20–22	Pravin M. Shah, MD	Echocardiography in the '80's: M-Mode vs. Two-Dimensional
318	April 23–25	Daniel S. Berman, MD	Nuclear Cardiology
319	April 27–28	Leonard S. Dreifus MD and Frits L. Meijler, MD	Computer Electrocardiology: Present Status and Hope for the Future
320	April 30 & May 1–2	John A. Spittell, MD	Peripheral Vascular Disease
321	May 6–8	Marvin I. Dunn, MD	Electrocardiography for Critical Care Nurses
322	May 11–13	Abdul J. Tajik, MD and James B. Seward, MD	The Role of Two-Dimensional Echocardiography in the Clinical Practice of Cardiology
323	May 14–16	G. Charles Oliver, MD	Ubiquitous PVC
324	May 18–20	William J. Mandel, MD	His Bundle Electrocardiography: Contributions to the Clinical Understanding of the Electrocardiogram
325	May 28–29	Robert O. Brandenburg, MD	Cardiology for the Consultant
326	June 1–3	Shahbudin H. Rahimtoola, MD	Valvular Heart Disease
328	June 8–10 (tentative)	Borys Surawicz, MD	Changing Role of Electrocardiography in the Clinical Practices
327	June 11–13	Robert G. Tancredi, MD	Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients
329	June 15–17	Robert A. O'Rourke, MD	Detection of Cardiac Disease by Physical Examination
302	June 22–24	Paul C. Gillette, MD	Decisions in Clinical Pediatric Cardiac Surgery
331	June 29–30, July 1	B. Leonard Holman, MD	Nuclear Cardiology
330	July 8–10	Michael R. Rosen, MD	Clinical Pharmacology and Electrophysiology of Antiarrhythmic Drugs

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ATIONS AND CONTRAINDICATIONS

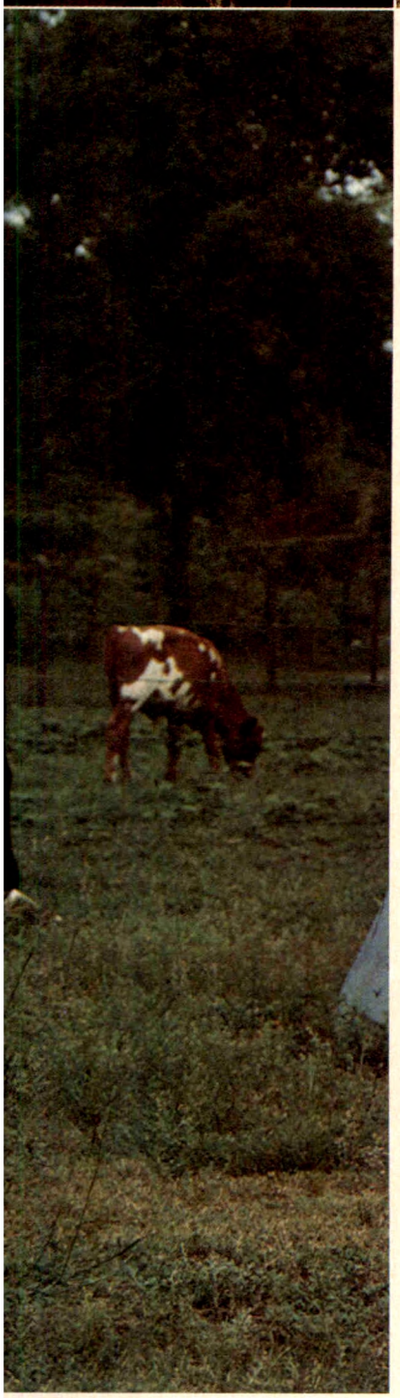
ndications for cardiac pacemaking are increasing as pace- become more sophisticated and as advanced methods for management become more widespread. Generally accepted ons for long-term cardiac pacing include but are not limited ck sinus syndrome; (2) chronic, symptomatic drug-resistant rhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of a myocardial infarction have not yet been rigorously defined. I to be considered include the location of the myocardial infa presence or absence of symptoms, ventricular rate, mechanis the arrhythmias, and response to therapy. In general, sympt drug-resistant bradyarrhythmias which impair cardiac outpu considered indications for pacing in patients with acute myo infarction, regardless of infarct location.









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Taking care of an 11-acre farm is no small task, but Wayne and his wife enjoy making it a family affair with their three children. And the children know that when the chores are all done, it's time for play. Wayne has his favorites—softball, water skiing, fishing, and hunting—and the rest of the family likes to get in on the action.

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henomena such as local tissue reaction or skin necrosis,
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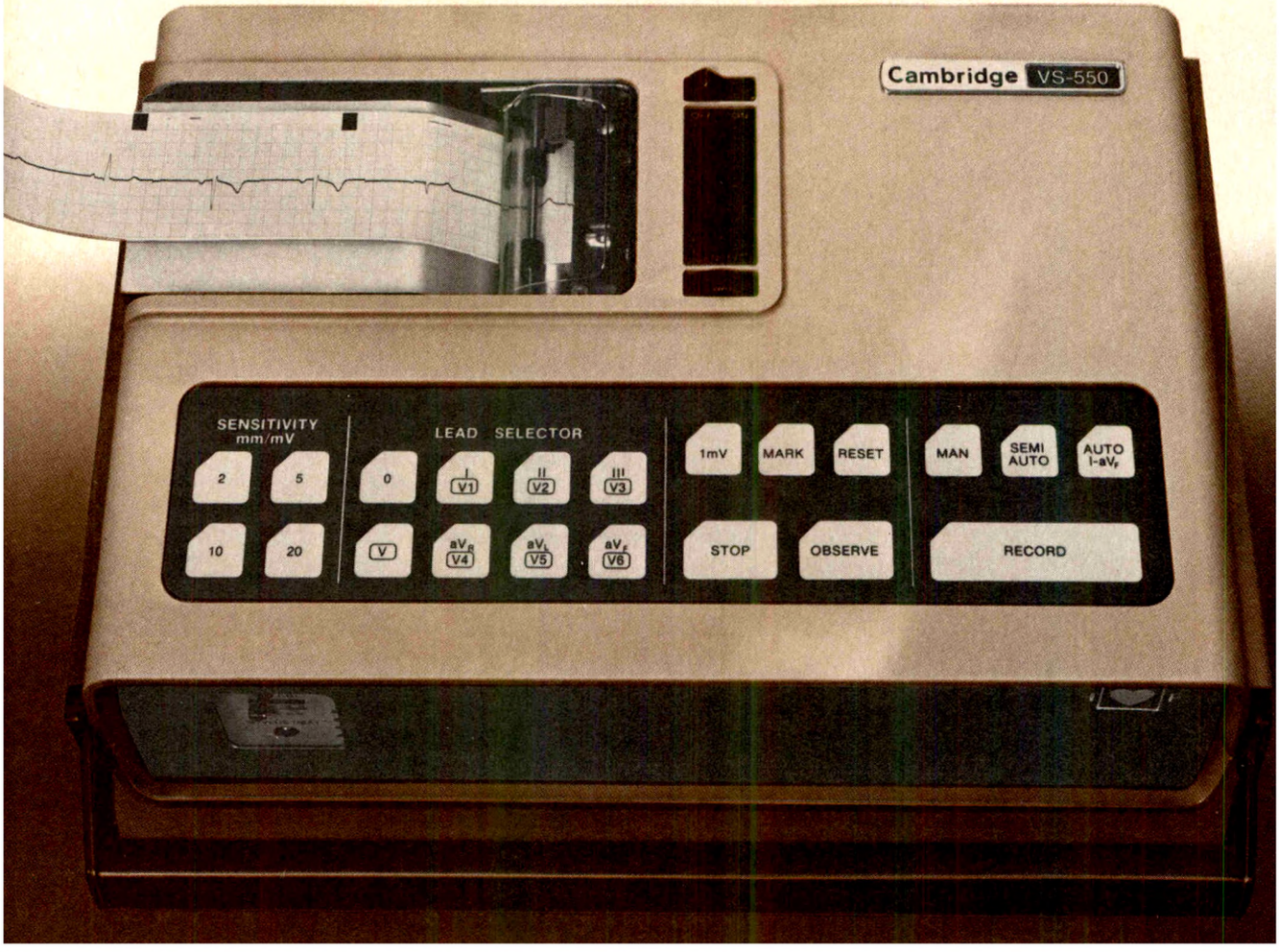
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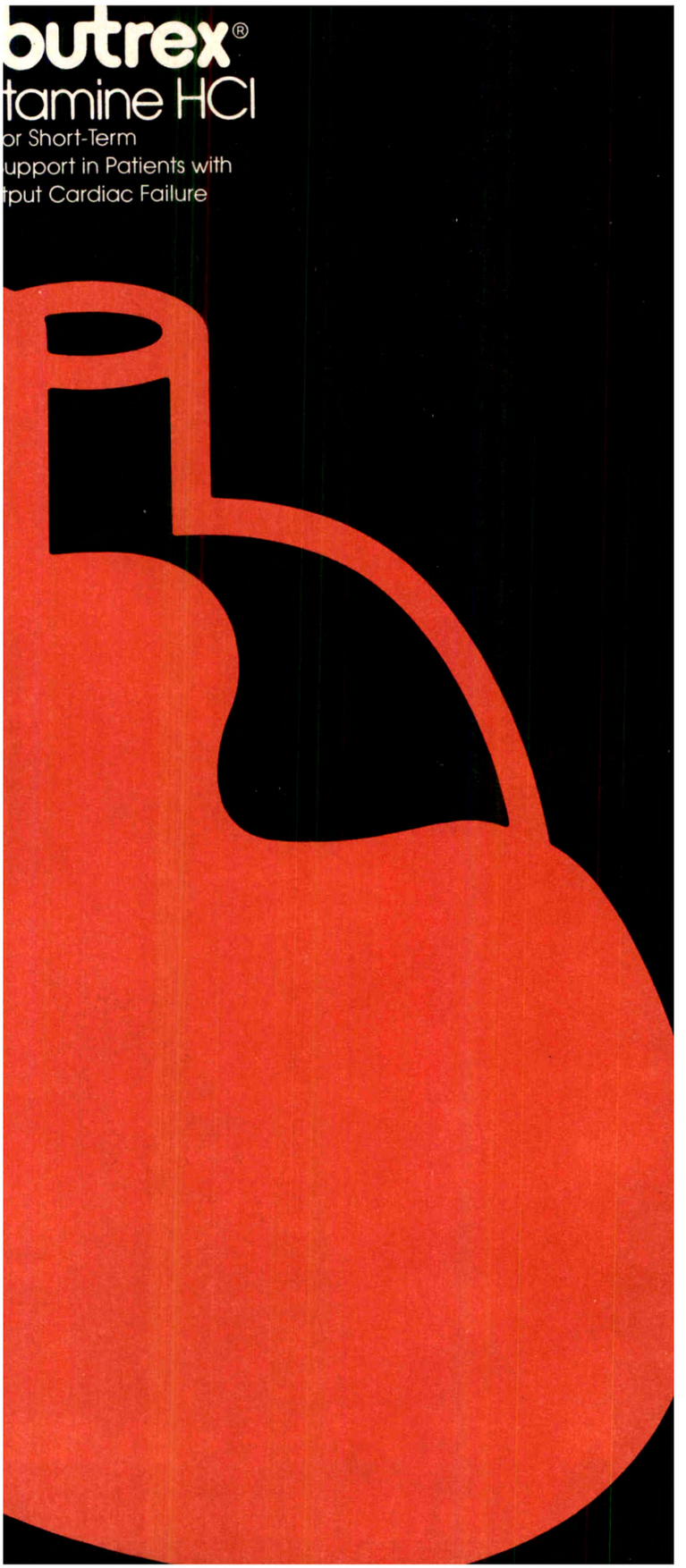
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)nsult the package literature for prescrib-
; information.

lications and Usage: Dobutrex® (do-
tamine hydrochloride, Lilly) is indicated
ien parenteral therapy is necessary for in-
opic support in the short-term treatment
adults with cardiac decompensation due
depressed contractility resulting either
m organic heart disease or from cardiac
gical procedures.
n patients who have atrial fibrillation with
)id ventricular response, a digitalis prep-
ation should be used prior to instituting
erapy with Dobutrex.

ntraindication: Dobutrex is contraindi-
ted in patients with idiopathic hyper-
phic subaortic stenosis.

rnings: 1. *Increase in Heart Rate or Blood*
essure—Dobutrex may cause a marked
:rease in heart rate or blood pressure,
)ecially systolic pressure. Approximately 10
rcent of patients in clinical studies have
d rate increases of 30 beats/minute or
)re, and about 7.5 percent have had a
-mm Hg or greater increase in systolic
essure. Reduction of dosage usually re-
rses these effects promptly. Because
butamine facilitates atrioventricular con-
ction, patients with atrial fibrillation are at
: of developing rapid ventricular response.
tients with preexisting hypertension ap-
ar to face an increased risk of developing
exaggerated pressor response.
2. *Ectopic Activity*—Dobutrex may precipi-
e or exacerbate ventricular ectopic ac-
ty, but it rarely has caused ventricular
:hycardia.

cautions: 1. **During the administration of**
butrex, as with any adrenergic agent, ECG
d blood pressure should be continuously
nitored. In addition, pulmonary wedge
essure and cardiac output should be
nitored whenever possible to aid in the
e and effective infusion of Dobutrex.
2. Hypovolemia should be corrected with
table volume expanders before treatment
h Dobutrex is instituted.
3. Animal studies indicate that Dobutrex
ay be ineffective if the patient has recently
:eived a beta-blocking drug. In such a
se, the peripheral vascular resistance may
:rease.
4. No improvement may be observed in
e presence of marked mechanical
struction, such as severe valvular aortic
nosis.
Usage Following Acute Myocardial
arction—Clinical experience with Dobu-
x following myocardial infarction has
en insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate		
	250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

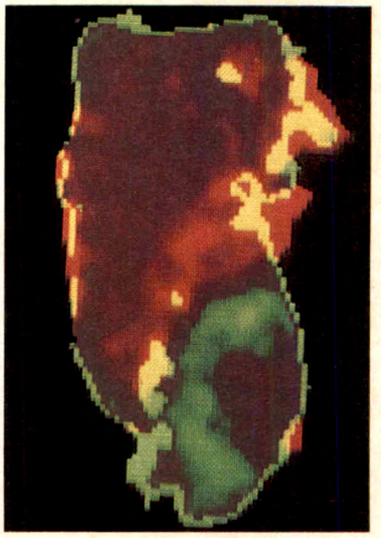
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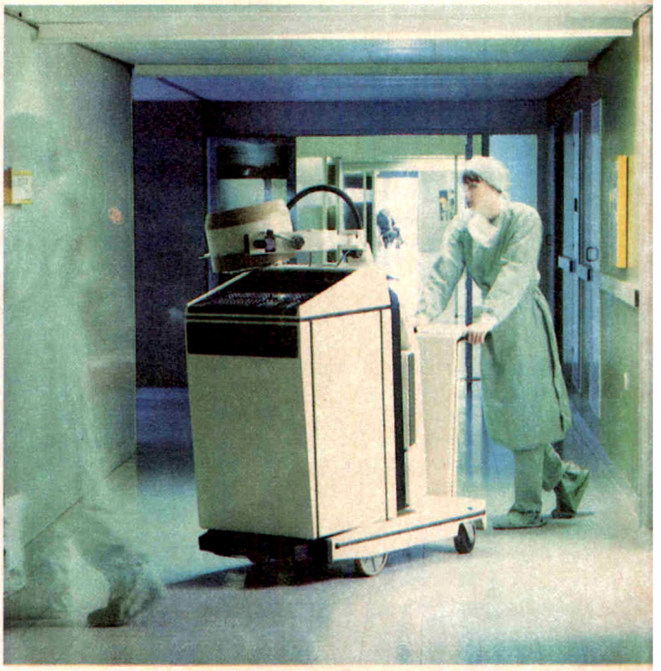
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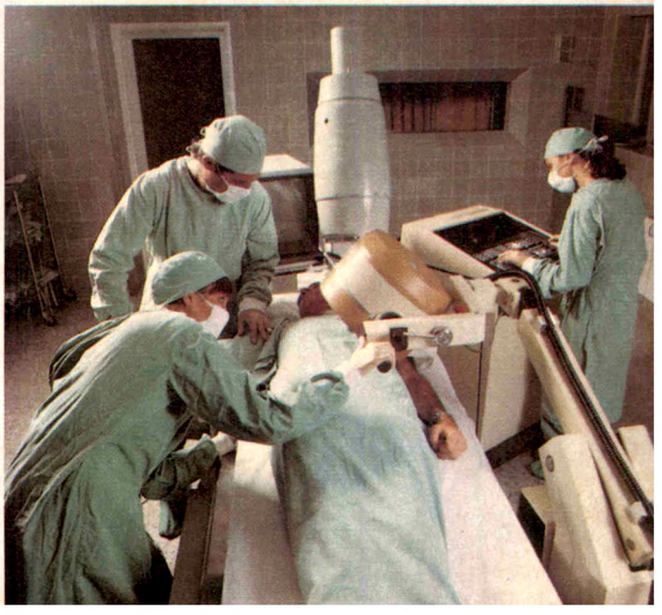
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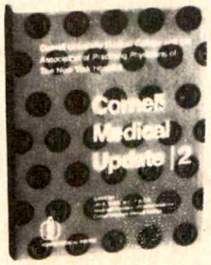
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5 ml AMPUL
5 ml ADDITIVE SYRINGE (Rap-Add™)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydro naturally-occurring biochemical catecholamine precursor of norepinephrine. It is a white crystalline powder, freely soluble in water and soluble in alcohol; sensitive to lig iron salts and oxidizing agents. *5 ml ampul and 5 ml additive syringe (Rap-Add).* sterile, non-pyrogenic INTROPIN contains 40 mg of dopamine hydrochloride (equivalent of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a pr

INDICATIONS: For the correction of hemodynamic imbalances present in the shock due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, re and chronic cardiac decompensation as in congestive failure.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnc by which adequacy of vital organ perfusion can be monitored. The physician sl observe the patient for signs of reversal of confusion or comatose condition. Loss increase in toe temperature and/or adequacy of nail bed capillary filling may als as indices of adequate dosage. Note that at doses above those optimal for the patient, urine flow may decrease, necessitating reduction of dosage. Concurrent a tion of INTROPIN and diuretic agents may produce a potentiating effect.

Low Cardiac Output – Increased cardiac output is related to the direct inotropic INTROPIN on the myocardium. Increased cardiac output at low or moderate doses associated with either static or decreased systemic vascular resistance (SVR) ar to be related to a favorable prognosis. Increase in cardiac output produced by is not associated with substantial decreases in SVR as may occur with isoproterenc

Hypotension – Hypotension due to inadequate cardiac output can be managed by a tion of low to moderate doses of INTROPIN, which have little effect on SVR therapeutic doses, the drug's alpha adrenergic activity becomes more prominent may correct hypotension due to diminished SVR. Administration should be cons soon as a definite trend toward decreased systolic and diastolic pressure become

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochro

WARNINGS: INTROPIN should not be administered in the presence of uncorrec arrhythmias or ventricular fibrillation. INTROPIN should not be added to any alkal solution since the drug is inactivated in alkaline solutions. Patients who have be with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN, v substantially reduced dosage (1/10 the usual starting dose).

Usage in Pregnancy – INTROPIN may be used in pregnant patients when, in the of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of INTROPIN for pediatric use has established.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovoler be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. decrease in the pulse pressure) is observed in patients receiving INTROPIN, the in should be decreased and the patient observed carefully for further evidence of p vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible the possibility of extravasation into tissue adjacent to the infusion site which r necrosis and sloughing of surrounding tissue. Large veins of the antecubital preferred to veins in the dorsum of the hand or ankle.

Occlusive Vascular Disease – Patients with a history of occlusive vascular di example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury endarteritis, and Buerger's disease) should be closely monitored for any change or temperature of the skin in the extremities.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and n in ischemic areas, the area should be infiltrated as soon as possible with 10 t of saline solution containing from 5 to 10 mg of Regitine® (brand of phentol an adrenergic blocking agent. A syringe with a fine hypodermic needle sh used, and the solution liberally infiltrated throughout the ischemic area. Symp blockade with phentolamine causes immediate and conspicuous local hyp changes if the area is infiltrated within 12 hours. Therefore, *phentolamine be given as soon as possible* after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Because of the arrhythmogenic potential of these agents and the known increase in cardiac irritability which may sensitize the myocardium, INTROPIN should be used with CAUTION in patients inhaling such anesthetics.

Careful Monitoring Required – As in the case of any adrenergic agent, ir INTROPIN should be accompanied by close monitoring of urine flow, cardiac blood pressure.

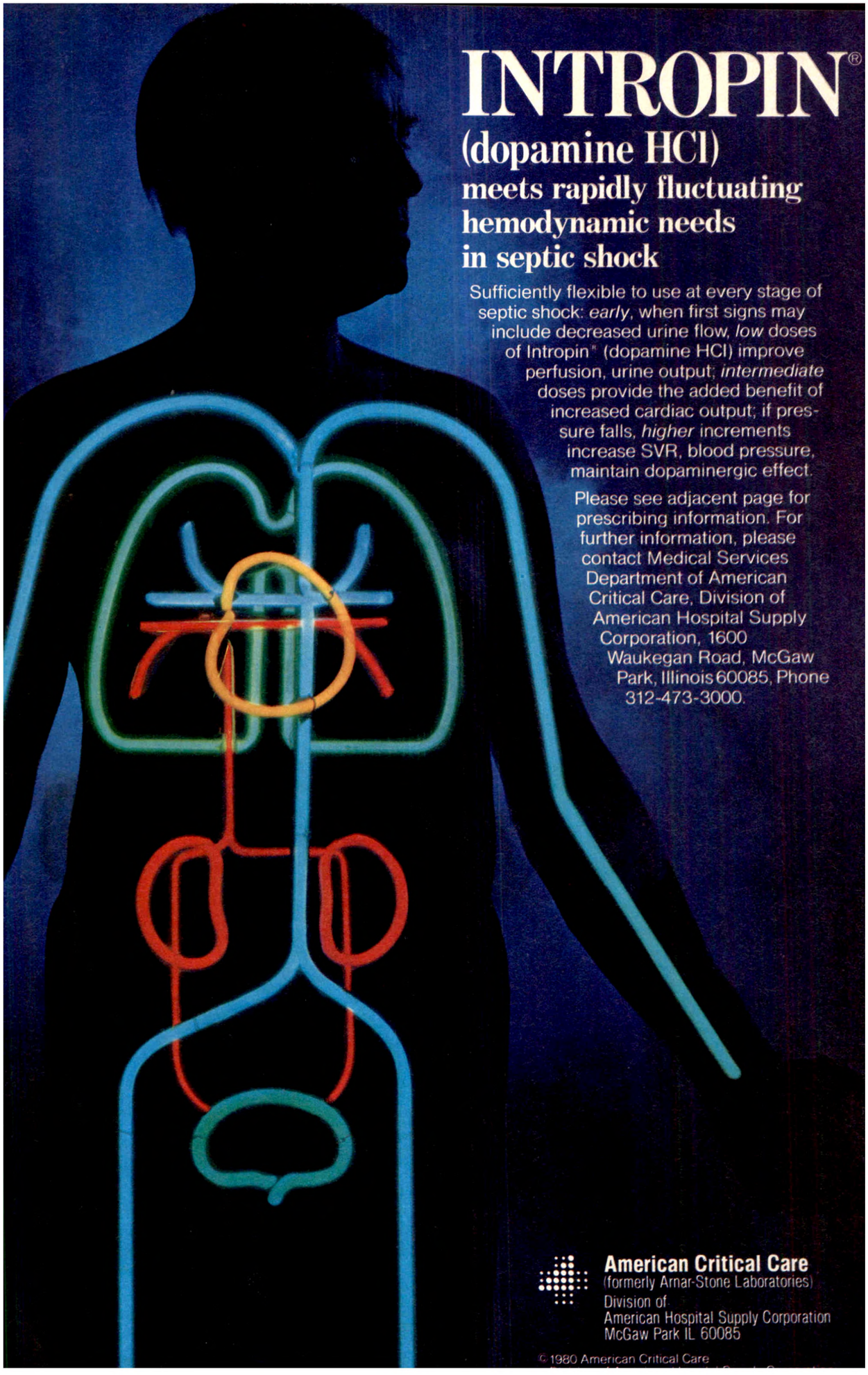
ADVERSE REACTIONS: The most frequent include ectopic beats, nausea, vomiti cardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoc Others reported infrequently are aberrant conduction, bradycardia, piloerection, wid complex, azotemia, and elevated blood pressure.

WARNING: This is a potent drug – must be diluted before administration to patient.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive bloo elevation, reduce rate of administration or temporarily discontinue INTROPIN unti condition stabilizes. Since the drug's duration of action is quite short, no additiona measures are usually necessary. If these measures fail to stabilize the patient's use of the short-acting alpha adrenergic blocking agent, phentolamine, should be c

CAUTION: Federal law prohibits dispensing without a prescription. Full direction should be read before administering or prescribing. Jan

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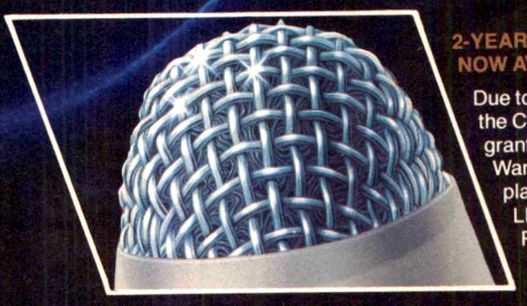
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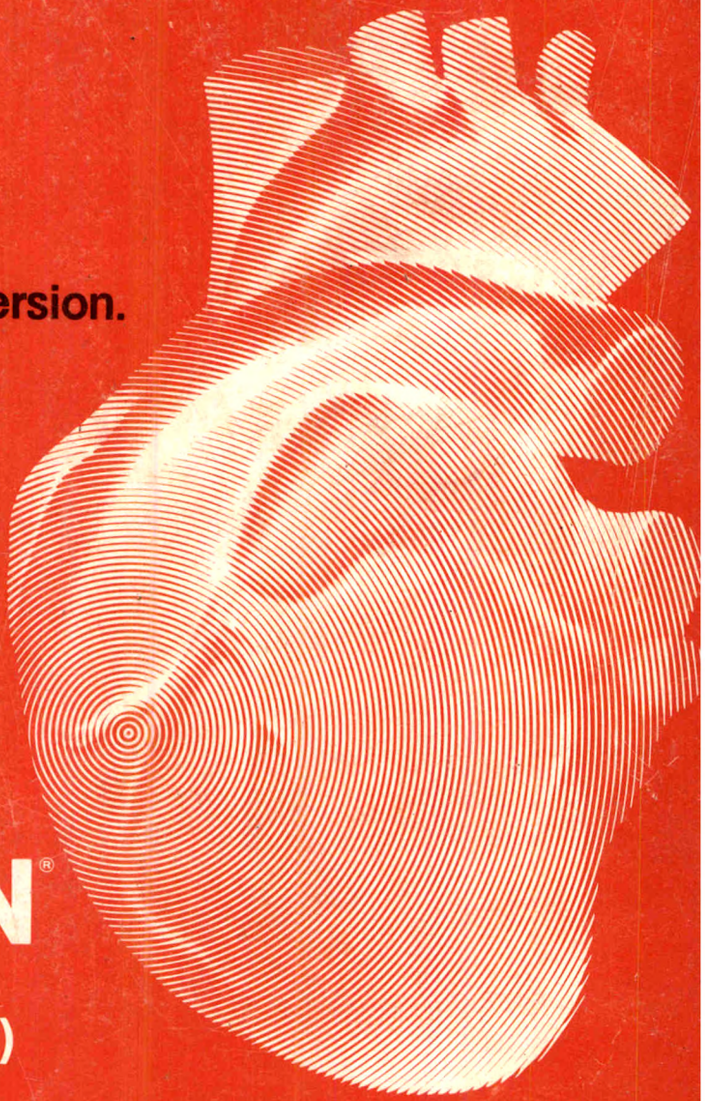
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(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion — only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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DECEMBER 1, 1980

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Predischarge Exercise Testing After Myocardial Infarction

Seminar on Calcium Channel Blockers—Part I

Eugene Braunwald, MD, FACC, Guest Editor

Index Issue

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ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

Cardiac output and blood pressure normally increase with increasing physical activity. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[1,2]

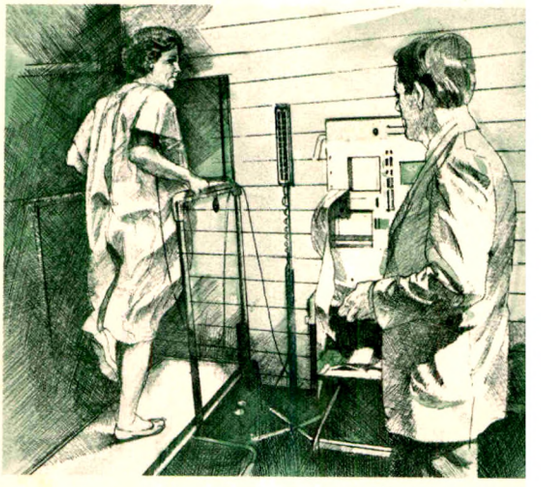
In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

Such findings can be of importance to active hypertensive patients such as the athletic individual or the person whose work requires substantial physical effort. For these and many other hypertensive patients, ALDOMET represents a logical therapeutic choice.

With ALDOMET, exercise hypotension rarely occurs. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

ALDOMET® offers many (METHYLDOPA|MSD) other important features:

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previc methyldopa therapy has been associated with liv disorders. It is important to recognize that a positi Coombs test, hemolytic anemia, and liver disorde may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorder could lead to potentially fatal complications unles properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hypertension by means of a graduated ergometric test, in Zanchett (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Clinic Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 56-63.

2. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatm with methyldopa on basal hemodynamics and on neural circ latory control, in Zanchetti A (ed): ALDOMET® (Methyldo MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.

3. Lee WR, Fox LM, Slotkoff LM: Effects of antihypertensive therapy on cardiovascular response to exercise. Am J Cardio 44:325-328, 1979.

For hypertension—

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(METHYLDOPA|MSD)
For a brief summary of prescribing information, please see following page.
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For hypertension—

ALDOMET®
(METHYLDOPA|MSD

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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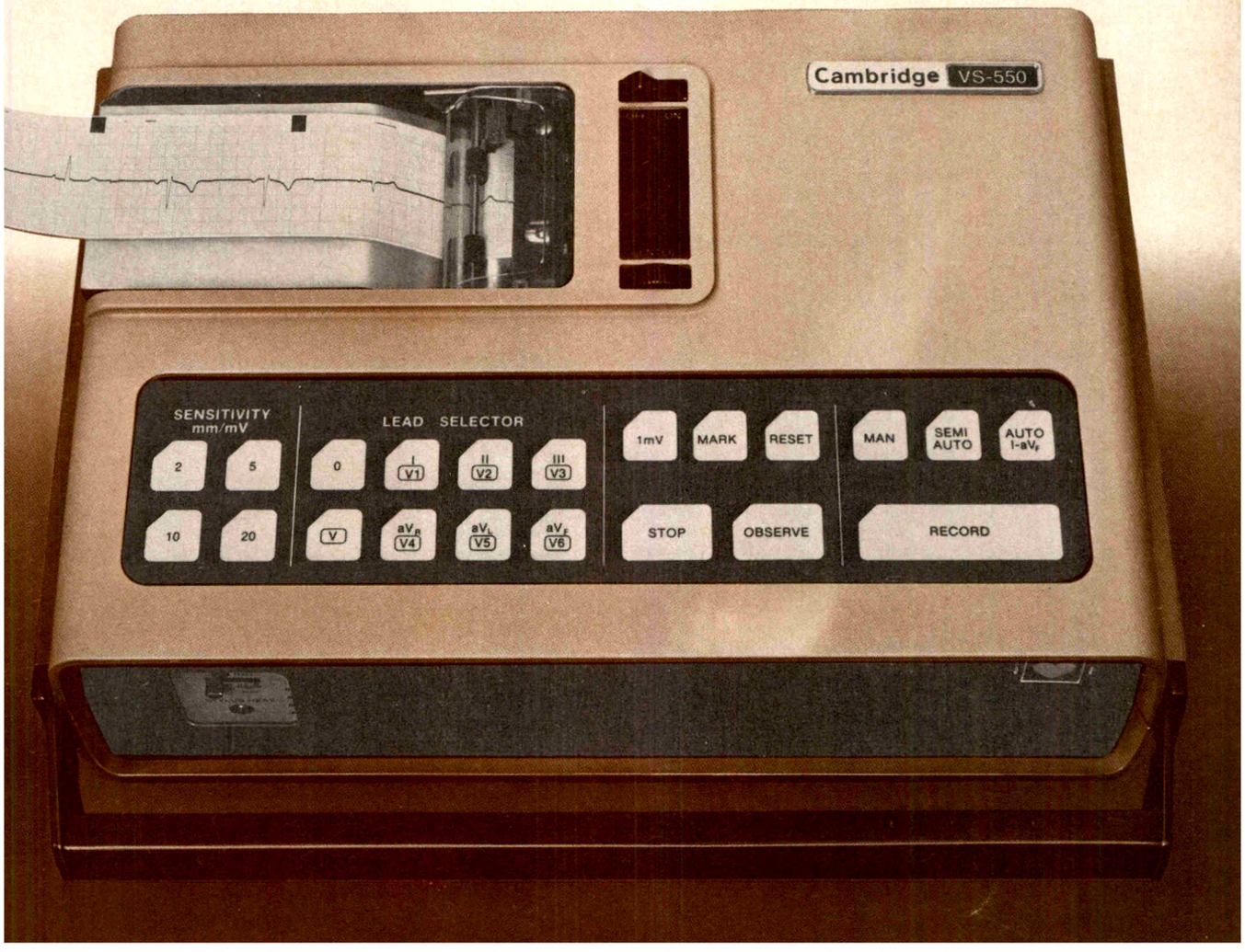
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Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

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Please see brief summary of prescribing information on adjoining page.

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Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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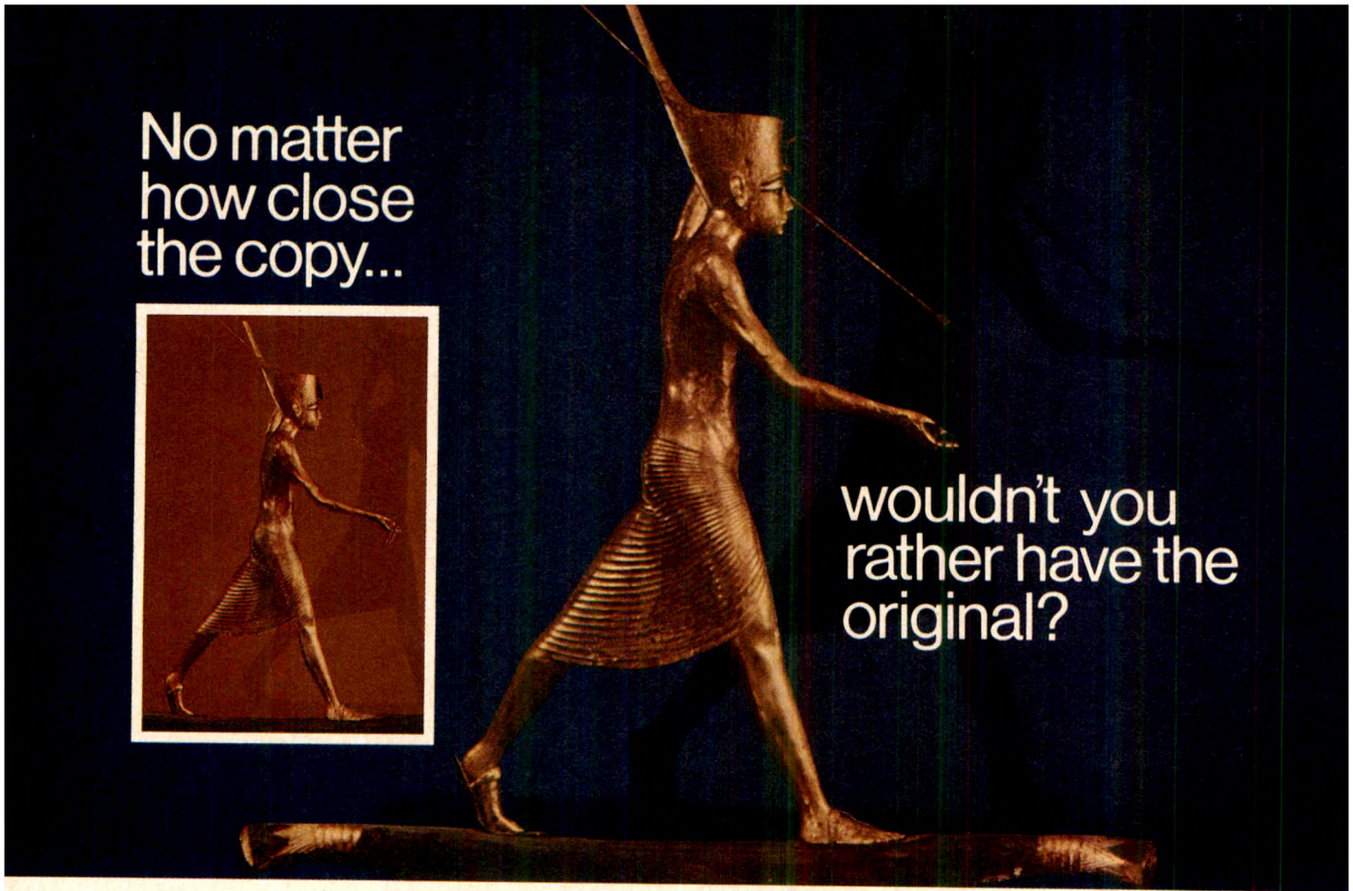
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"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS— Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg and 75 mg

For complete details, please see the full prescribing information.

Boehringer Ingelheim Ltd.
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DECEMBER 1980

The American Journal of CARDIOLOGY®

VOLUME 46

NUMBER 6

CONTENTS

CLINICAL STUDIES

909 Exercise Testing Early After Myocardial Infarction: Predictive Value for Subsequent Unstable Angina and Death

MARK R. STARLING, MICHAEL H. CRAWFORD, GEMMA T. KENNEDY and ROBERT A. O'ROURKE

Modified treadmill exercise testing before hospital discharge in 130 patients with uncomplicated myocardial infarction revealed that 60 percent had one or more treadmill exercise-induced abnormalities, including S-T segment depression, angina and inadequate blood pressure response. Such patients had a significantly greater incidence of all cardiac events during the follow-up period of 6 to 20 months when compared with patients without such treadmill abnormality. These three abnormalities identify patients with uncomplicated myocardial infarction who are at risk for a future cardiac complication. During the 6 to 20 month period after myocardial infarction, cardiac death occurred only in patients with a treadmill exercise-induced abnormality. Patients with such treadmill exercise-induced abnormalities merit closer medical follow-up and further diagnostic and therapeutic interventions designed to alter their poor prognosis.

915 Noninvasive Identification of a High Risk Subset of Patients With Acute Inferior Myocardial Infarction

PREDIMAN K. SHAH, MAX PICHLER, DANIEL S. BERMAN, JAMSHID MADDAHI, THOMAS PETER, BRAMAH N. SINGH and H. J. C. SWAN

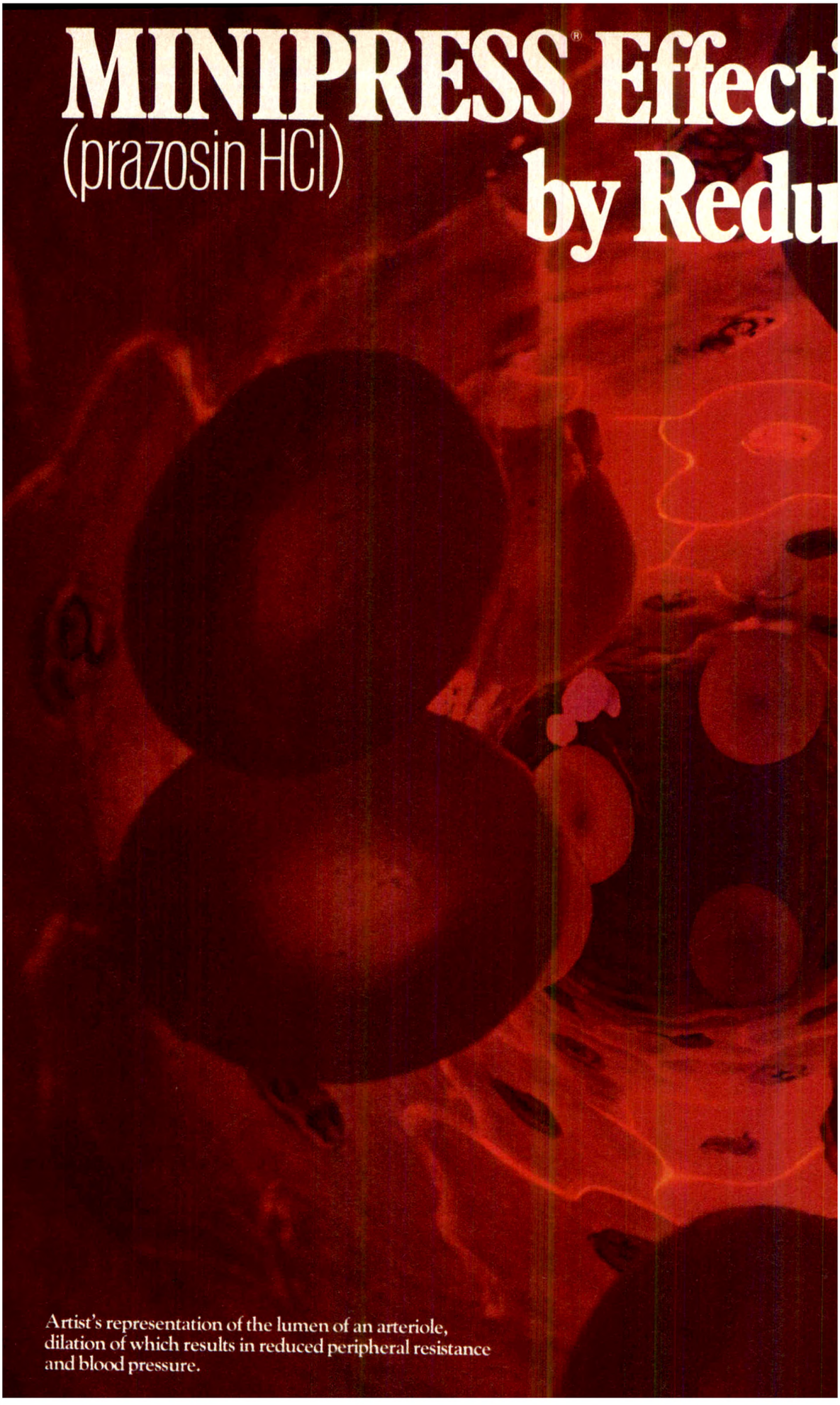
Noninvasive measurement of left ventricular ejection fraction and regional wall motion with radionuclide ventriculography in 44 patients within 48 hours of the onset of acute transmural inferior infarction indicates that such patients who have associated precordial S-T segment depression have greater impairment of global and regional left ventricular function presumably due to associated ischemia or infarction in areas remote from the inferior wall. They also have relatively high in-hospital mortality and morbidity rates. This study also demonstrated a high degree of correlation between S-T segment depression in precordial leads and the presence of regional dyssynergy in noninfarcted segments. The in-hospital clinical course of patients with a depressed left ventricular ejection fraction was characterized by a high incidence rate of postinfarction ischemic chest pain, pump dysfunction and mortality. Although these results show that a high risk subset of patients with inferior myocardial infarction can be characterized noninvasively, no data are as yet available to suggest that aggressive therapy may alter their morbidity and mortality.

922 Ergonovine Testing in a Coronary Care Unit

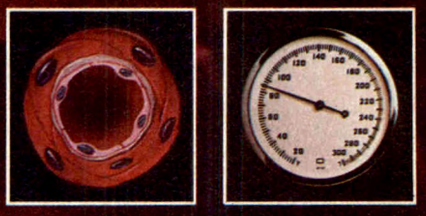
DAVID D. WATERS, PIERRE THEROUX, JADWIGA SZLACHCIC, FRANZ DAUWE, JEAN CRITTIN, RAOUL BONAN and HENRY F. MIZGALA

Ergonovine testing in 100 consecutive patients in a coronary care unit proved useful and was positive in all 17 patients with known variant angina and in 18 (40 percent) of 45 patients with chest pain suggestive of variant angina but no electrocardiogram recorded during the bout of pain. A small but definite incidence of serious complications, including ventricular arrhythmias, severe transient hypotension, recurrent angina and a subendocardial infarction, occurred during a positive test. On the basis of these data, the authors recommend that (1) ergonovine

continued on page A16


MINIPRESS® Effecti
(prazosin HCl)
by Redu
Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension
Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

MINIPRESS®

(prazosin HCl)

Capsules 1 mg, 2 mg, 5 mg

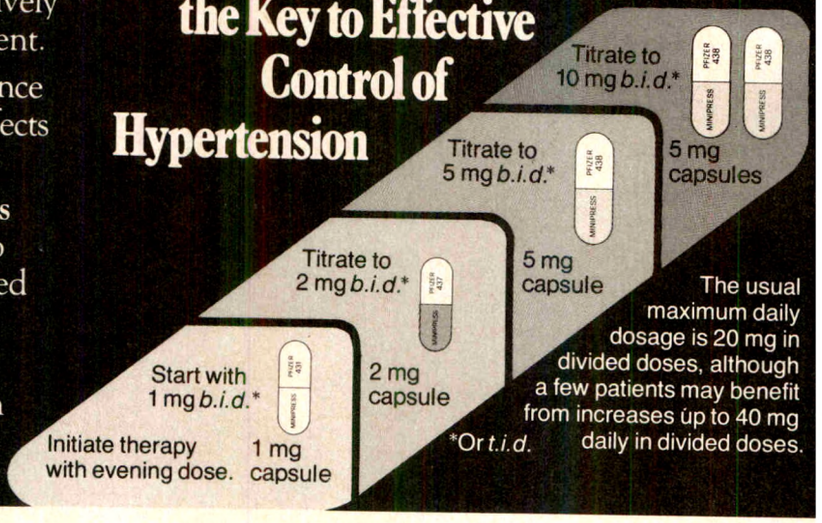
Please see Brief Summary on last page.

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MINIPRESS®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure by reducing peripheral resistance.**
- **Maintains cardiac output** which allows patients to maintain an active life style.
- **Maintains renal blood flow and glomerular filtration rate** so it can be used effectively even in patients with renal impairment.
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



The usual maximum daily dosage is 20 mg in divided doses, although a few patients may benefit from increases up to 40 mg daily in divided doses.

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

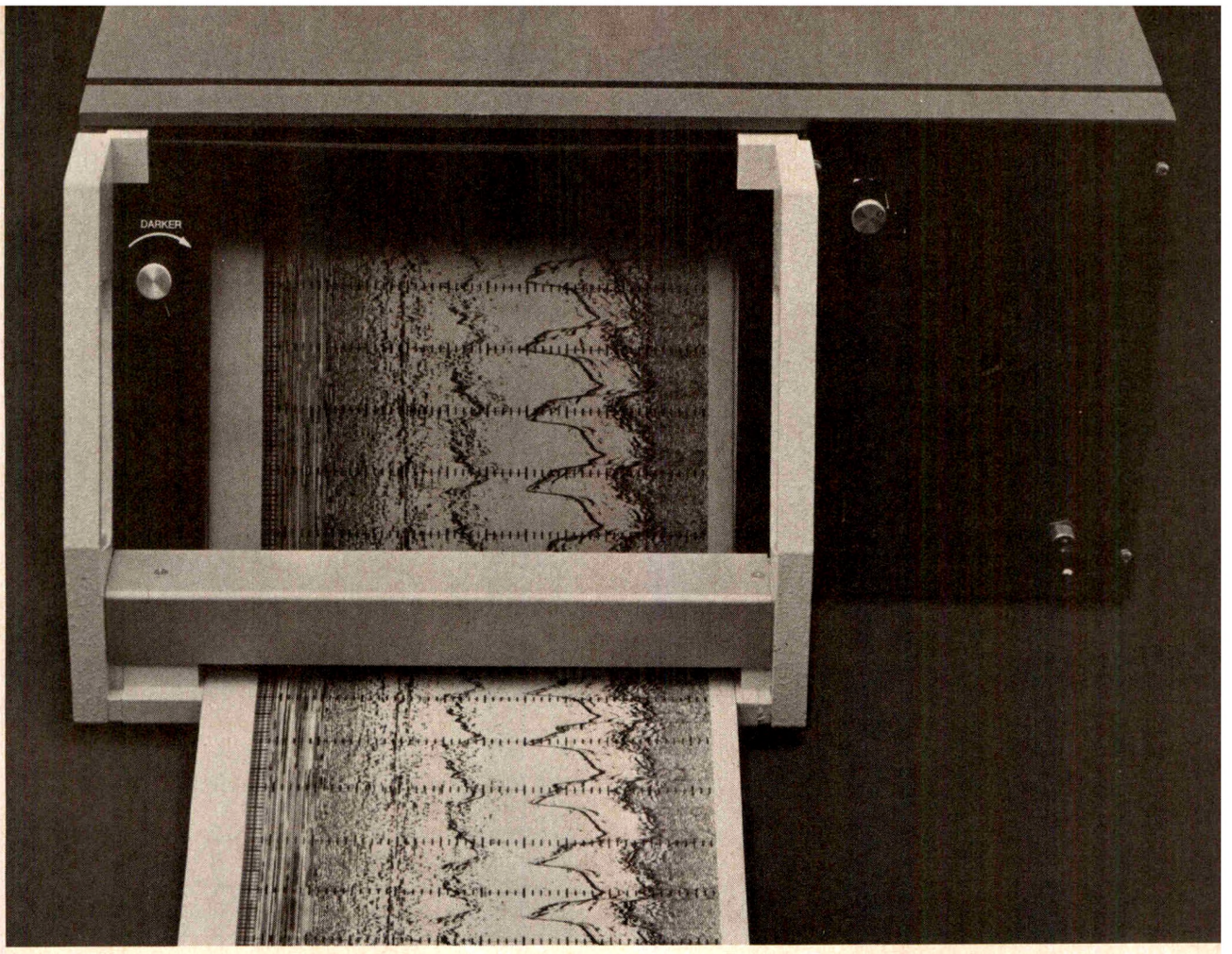
HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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PFIZER INC.



TAKE A LOOK AT HONEYWELL'S NEW RECORDER AND SEE WHAT YOU'VE BEEN MISSING IN ECHOCARDIOGRAMS.

If you're not seeing everything you expect from your present system, you should be looking at the LS-8—a totally new concept in presenting diagnostic information for echocardiography.

It delivers crisp black and white echocardiograms that won't fade. Echocardiograms that are developed dry, without chemicals, and without any warm-up delay caused by speed changes. So you get an instant echocardiogram for immediate evaluation.

And what an echocardiogram! Sharp and clear, with automatic intensity compensation for paper speeds from 5 to 100 mm/sec and the kind of high resolution and superior contrast that comes only from a wide and accurate gray scale range. Optional with direct print paper at 5 to 500 mm/sec.

Specific application modules provide optimum performance in a wide variety of applications, including M-mode echo, video for real time, and B-scan. Other modules can interface with up to six physiological data channels and provide timelines. The 2 kHz frequency response of the data channels provides diagnostic-quality phonocardiography recordings. And since the LS-8 is convection-cooled, there's no fan noise, no acoustical interference on sensitive phonocardiography channels.

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Honeywell's new LS-8 Stripchart Recorder will deliver every bit of image quality your ultrasound system is capable of. Ask your echo system supplier. Or contact Bob Shipman, Honeywell Test Instruments Division, Dept. AJC, Box 5227, Denver, Colorado 80217, phone 303/773-4700.

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A

testing be performed either in a coronary care unit environment in patients with known coronary anatomy or during coronary arteriography; (2) patients with multiple severe fixed coronary obstructions not be tested; (3) the initial ergonovine dose be limited to 0.0125 or 0.015 mg; (4) that ergonovine not be administered more often than at 5 minute intervals; and (5) patients with angina with S-T elevation during the test be treated immediately with intravenous or intracoronary nitroglycerin.

931 Clinical Relevance of Exercise-Induced S-T Segment Elevation

GARY L. STILES, ROBERT A. ROSATI and ANDREW G. WALLACE

The previously reported association between wall motion abnormalities and exercise-induced S-T elevation appears to be a function of the patient group studied. In patients in this study without prior myocardial infarction the cause of exercise-induced S-T elevation or depression did not appear to be related to the severity of the coronary lesions, ventricular function or wall motion abnormalities at rest. In patients with prior myocardial infarction exercise-induced S-T elevation appeared to be a marker of depressed left ventricular function such as poorer myocardial contractility, reduced ejection fraction and more aneurysm formation. The role of coronary spasm in the production of exercise-induced S-T elevation could not be defined.

937 Nonfatal Myocardial Infarction in Medically Treated Patients With Coronary Artery Disease

PHILIP J. HARRIS, FRANK E. HARRELL, Jr., KERRY L. LEE and ROBERT A. ROSATI

Left ventricular function, specific coronary anatomy, previous myocardial infarction and age proved the most important patient discriminators associated with nonfatal myocardial infarction as the first event after cardiac catheterization in 1,214 medically treated patients with coronary artery disease. In any subset of patients with a uniform risk of ischemic events (nonfatal infarction or death), nonfatal infarction is most likely to occur in those who are young, have had no previous infarction, have subtotal left anterior descending and right coronary arterial stenosis and normal hemodynamics. In patients less than 45 years old, 57 percent of the events were nonfatal; in patients 55 years and older, only 27 percent were nonfatal.

943 Platelet Function Studies in Coronary Heart Disease. IX. Increased Platelet Prostaglandin Generation and Abnormal Platelet Sensitivity to Prostacyclin Endoperoxide Analog in Angina Pectoris

JAWAHAR MEHTA, PAULETTE MEHTA and C. RICHARD CONTI

This study in 22 patients aged 44 to 71 years with a history of angina pectoris suggests that increased platelet prostaglandin generation and abnormal platelet sensitivity to prostacyclin and endoperoxide analog are important potential mechanisms in the pathogenesis of myocardial ischemia and may have important pathophysiologic implications. Platelet malondialdehyde production was higher in these patients with angina pectoris than in control subjects. Their platelets were significantly less sensitive to prostacyclin's antiaggregatory effects and less epoxymethanodienoic acid was required to induce 50 percent platelet aggregation than in the normal subjects. The important implications of these findings in the pathogenesis of myocardial ischemia are discussed.

948 Electrophysiologic and Hemodynamic Studies in Patients Resuscitated From Cardiac Arrest

MARK E. JOSEPHSON, LEONARD N. HOROWITZ, SCOTT R. SPIELMAN and ALLAN M. GREENSPAN

Electrophysiologic studies performed in 52 patients resuscitated from cardiac arrest reveal ventricular tachycardia often precipitated cardiac arrest in these subjects. In those in whom ventricular tachycardia or fibrillation was induced in the laboratory, cardiac catheterization revealed more marked impairment of hemodynamic function, more severe coronary disease, lower mean cardiac index, higher left ventricular end-diastolic pressure and lower ejection fraction than in those in whom no arrhythmia could be induced. Coronary artery disease was present in 23 of 28 patients with inducible arrhythmias. The initiating mechanism of the cardiac arrest in the 19 patients in whom no ventricular tachyarrhythmias were induced remains uncertain. The lack of success of the empiric use of antiarrhythmic drugs to prevent sudden death most likely results from the incorrect choice of antiarrhythmic agent, inadequate dosage, poor patient compliance or all three. Electrophysiologic testing may pro-

continued on page A20



CHEWABLE SORBITRATE®

(ISOSORBIDE DINITRATE) 5 mg. or 10 mg.

dependable, prolonged protection during periods of emotional or physical exertion.

Summary Of Prescribing Information

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.
Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.
Precautions: Tolerance and cross tolerance to other nitrates may occur.
Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.
Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE® (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.
Onset of Effect: Two to five minutes.
Duration of Effect: One to two hours.

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...other reason were called PACESETTER:

Pacesetter® Introduce
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6 3



Programalith 6 is the full six-parameter interrogatable, programmable pacemaker. In conjunction with the Programmer, Programalith 6 provides the physician with the means for comprehensive paced-patient management while obviating many common reasons for invasive pacing system revision.



For less critical applications, Programalith 3 provides the physician with the same basic interrogation capabilities as Programalith 6 as well as three programming functions – pacing rate, pulse width and sensitivity – all with multiple options.

Only after you have reached the ultimate in sophistication can you truly simpli
This new 6-3-1-0 family of Programalith® Interrogatable™ pacemakers is ide
demonstration of that fact. It is the most flexible system ever offered the physicia
Even the simplest of these four pulse generators offers the all-important Pacesett
exclusive: a simple method of calculating years of remaining battery capac
as well as an accurate determination of possible problems and their locatio
through measurement by interrogation of lead and heart interface impedanc

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a Complete Family of Pacemakers.

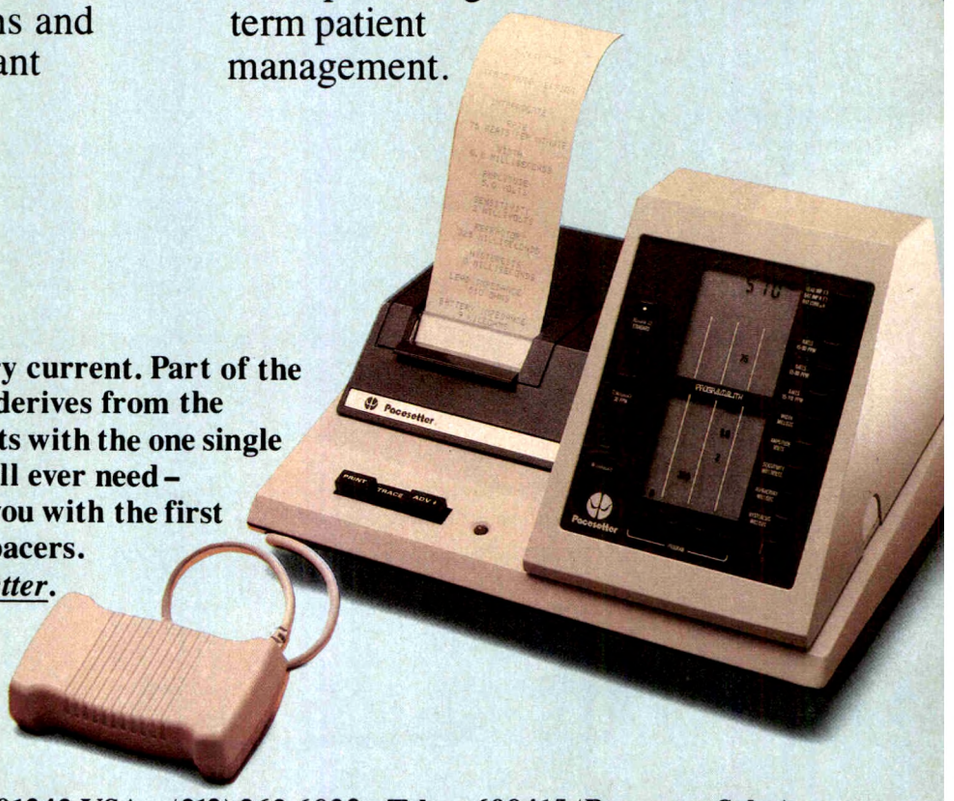


Programalith 1 interrogates and programs a single parameter – pacing rate – allowing the physician to choose from 12 different options and provides the all-important interrogation function as well.



For simplest applications, Programalith 0 requires no programming, yet can still be interrogated for all measured data, providing invaluable assistance in lon term patient management.

battery impedance and battery current. Part of the flexibility of this new system derives from the complete integration of all units with the one single programmer the physician will ever need – the one Pacesetter supplies to you with the first implant of any one of these pacers. No wonder they call us Pace*setter*.



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vide data on which to base more successful therapy, medical or surgical, in patients resuscitated from cardiac arrest.

956 Amount of Narrowing by Atherosclerotic Plaque in 44 Nonbypassed and 52 Bypassed Major Epicardial Coronary Arteries in 32 Necropsy Patients Who Died Within 1 Month of Aortocoronary Bypass Grafting

BRUCE F. WALLER and WILLIAM C. ROBERTS

In 32 necropsy patients who died within 30 days of an aortocoronary bypass operation for relief of angina pectoris, the lumens in 42 (95 percent) of 44 nonbypassed and in all 52 bypassed arteries were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque. This study further demonstrated not only that the necropsy patients with angina pectoris who died soon after operation had diffuse coronary atherosclerosis, but also that their preoperative angiograms frequently underestimated the severity of their coronary narrowing.

963 Results of Operation for Obstructive Hypertrophic Cardiomyopathy in the Elderly: Septal Myotomy and Myectomy in 20 Patients 65 Years or Older

JEAN-PAUL KOCH, BARRY J. MARON, STEPHEN E. EPSTEIN and ANDREW G. MORROW

These results of operative treatment in 20 patients with hypertrophic cardiomyopathy 65 year of age and older show that septal myotomy and myectomy can produce gratifying symptomatic and hemodynamic improvement. Operation decreased markedly or abolished the left ventricular gradient in the 17 patients who underwent postoperative cardiac catheterization. Sixteen of the 18 long-term survivors have had persistent and significant functional improvement for up to 6 years after surgery, including 7 patients who are now asymptomatic. One patient died on the second postoperative day and complete heart block developed in two others. Septal myotomy and myectomy should be considered in patients over the age of 65 who do not obtain symptomatic benefit from propranolol or verapamil. Morbidity and mortality from operation were not greater in older patients than in those operated on earlier in life.

EXPERIMENTAL STUDIES

967 Lidocaine-Induced Reduction in Size of Experimental Myocardial Infarction

FRED N. NASSER, JOSEPH T. WALLS, WILLIAM D. EDWARDS and CARLOS E. HARRISON, Jr.

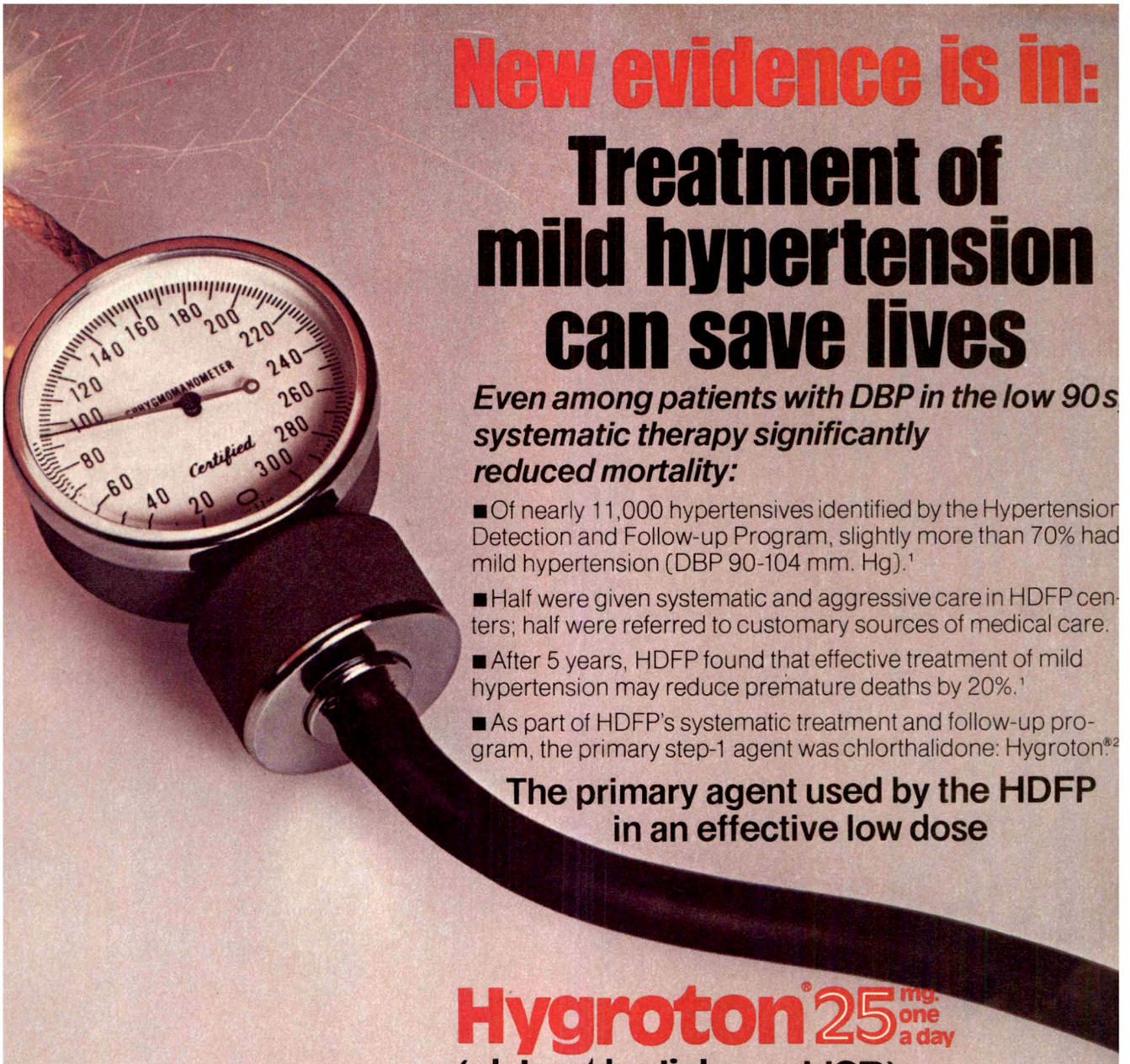
In these anesthetized open chest dogs subjected to 40 minutes of occlusion of the left anterior descending artery, followed by 5 hours of reperfusion, the infusion of lidocaine significantly reduced the size of the experimentally produced myocardial infarction, probably by reduction of oxygen utilization. These experiments demonstrated a decrease in mitochondrial state 3 respiratory rate after the administration of lidocaine. The reduction of myocardial infarct size did not depend on enhanced myocardial flow and was independent of left ventricular stroke work. Pretreatment with lidocaine is not needed to decrease infarct size or to permit lidocaine to reach the ischemic zone. As a result, lidocaine therapy to preserve ischemic myocardial cells could potentially be given to patients who have acute coronary insufficiency before or early in the course of myocardial infarction.

976 Comparison of Multigated Radionuclide Angiography With Ultrasonic Sonomicrometry Over a Wide Range of Ventricular Function in the Conscious Dog

JUDITH L. SWAIN, KENNETH G. MORRIS, FREDERICK P. BRUNO and FREDERICK R. COBB

Comparing the simultaneous, noninvasive assessment of left ventricular function by multigated radionuclide angiography with that obtained with ultrasonic sonomicrometry in six conscious dogs, these investigators found that the former technique reliably assessed changes in ejection fraction and dV/dt over a wide range of ventricular function. There was a good correlation between the two techniques. In general, however, radionculide angio-

continued on page A24



New evidence is in:

Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90s, systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertension Detection and Follow-up Program, slightly more than 70% had mild hypertension (DBP 90-104 mm. Hg).[1]
- Half were given systematic and aggressive care in HDFP centers; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.[1]
- As part of HDFP's systematic treatment and follow-up program, the primary step-1 agent was chlorthalidone: Hygroton®.[2]

The primary agent used by the HDFP in an effective low dose

Hygroton® 25 mg. one a day
(chlorthalidone USP)

Because there's nothing mild about mild hypertension

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.
Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

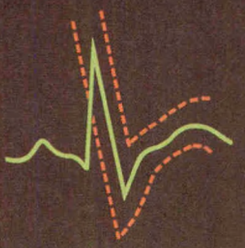
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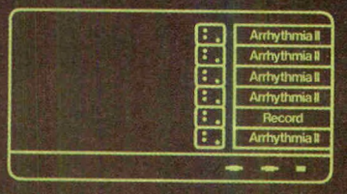
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No other arrhythmia detection system gives you all this:

1



2



Dramatically reduced false alarms

We start with template matching—the preferred method—to discriminate between the patient's dominant beat and ectopics. But only Arrhythmia II adds two unique features to screen out artifact, ensuring that only qualified ectopic activity triggers alarms or is included in trends: (1) each abnormal beat must appear four times before it's accepted as a "true" ectopic class, and (2) our "over-range" circuitry suspends ECG processing for a minimum of five seconds when it detects excessive noise.

MEMORY BANK OF CLASSES		NUMBER OF OCCURRENCES 1	2	3	4	5	6	7 →
C-0	NORMAL	*	*	*	*	*	*	*
C-1		•	•	•	•	*	*	
C-2		•	•					
C-3		•						
C-4		•	•	•	•	*		
C-5		•						
C-6								
C-7								
C-8								
C-9								
C-10								
C-11								
C-12								
C-13	COUPLET							
C-14	DROPPED BEAT							
C-15	PACED							

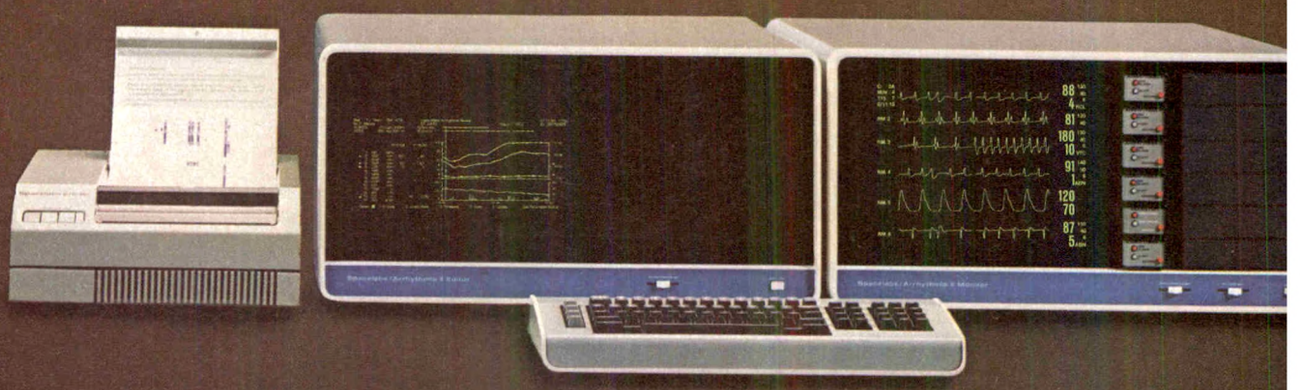
4-MATCH CRITERIA

More meaningful patient information

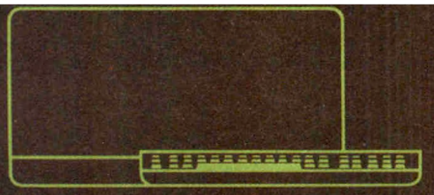
Other computerized arrhythmia detection systems may accurately detect and record ectopic activity. But we just start there. Only Arrhythmia II allows you to select those ectopics that are particularly important for a patient and to include only those ectopics in trends. You can quickly recall classes of ectopics and their frequency over 24 hours. And, on the Editor, you can trend a specific class or combination of classes for 1, 2, 8 or 24 hours, without having to edit out each occurrence of unwanted information.



Arrhythmia II



3

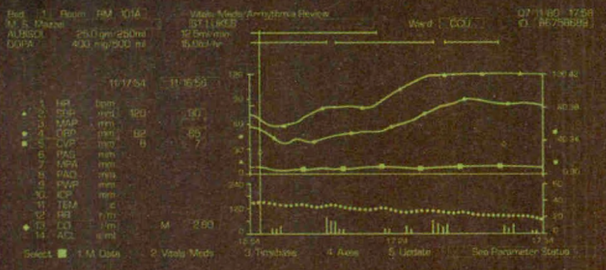


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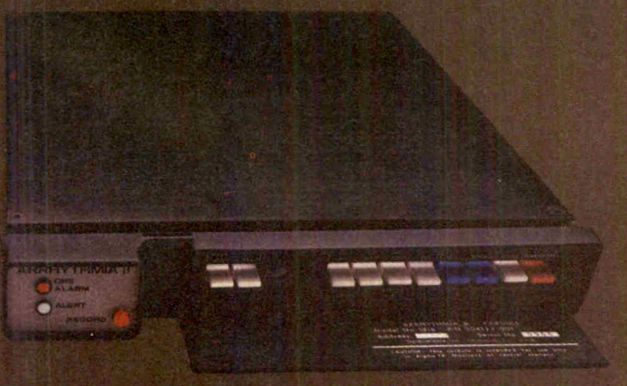
See effects of treatment on one screen

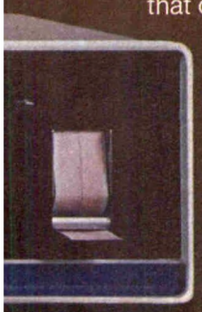
Only Arrhythmia II lets you trend medications, ectopics and vital signs on one display, in a concise and easy-to-interpret format. And it provides 24-hour recall so the precise information on ectopics, vital signs and medications is available for any specific time.



A computer for each patient

Hospitals using minicomputer systems have experienced the loss of critical data on all patients connected to the system when the computer malfunctions. But that can't happen with Arrhythmia II, because each patient has his own computer. And any malfunction only affects that one patient. The microprocessor-based cardule can then be replaced in minutes and easily repaired by simply inserting a new circuit board.





We designed Arrhythmia II to solve clinical problems that other arrhythmia systems have not even tried to solve. We feel it represents our care and concern in applying technology to the clinical setting—an approach that has made Spacelabs the fastest growing company in patient monitoring today.

But you don't have to take our word for it. Call us today (213-882-9560, collect) to arrange for an evaluation in *your* hospital. Then we think you'll agree with the growing number of your colleagues who believe that Arrhythmia II is the best system available.

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graphic measurements overestimated the ejection fraction by comparison with sonomicrometric measurements and the overestimation increased as ejection fraction increased.

METHODS

983 Tricuspid Regurgitation in Tricuspid Valve Prolapse Demonstrated With Contrast Cross-Sectional Echocardiography

CHIN C. CHEN, JOEL MORGANROTH, T. JOSEPH MARDELLI and MASAHITO NAITO

Contrast cross-sectional echocardiography proved reliable for identifying tricuspid regurgitation with a high degree of specificity and sensitivity. Patients with tricuspid valve prolapse had a 40 percent prevalence rate of tricuspid regurgitation. These patients require careful follow-up care. In patients with minimal or low pressure tricuspid regurgitation, whose murmur is usually not holosystolic and is nonspecific in character, cross-sectional echocardiography with contrast enhancement appears to provide a sensitive and specific means of diagnosing tricuspid regurgitation.

988 Body Surface Distribution of Exercise-Induced QRS Changes in Normal Subjects

DAVID M. MIRVIS

Analysis of the anterior thoracic isopotential distributions of the electrocardiogram at rest and during exercise at 85 percent of maximal heart rate in 30 normal male volunteers showed (1) reduction in peak positive potential at rest but not at all instants in the QRS complex without a shift in extrema location; (2) an increase in peak negative potential at all time points in most subjects; (3) the location-dependent nature of the R and S waves and QRS complex amplitude changes in individual hearts; and (4) continuity of QRS changes spatially but not in magnitude with those detected during other portions of the cardiac cycle. Exercise reduced the positive forces and augmented negative voltages at most anterior thoracic sites but did not significantly alter the location of map extrema. Difference maps suggest that exercise generated an electrical field characterized by a central anterior maximum bordered superiorly by positive potentials. It appears unlikely that changes in intracavitary blood mass and atrial repolarization are solely responsible for the effects observed in this study.

997 Improved Catheter for Regional Coronary Sinus Flow and Metabolic Studies

DONALD S. BAIM, MARTIN T. ROTHMAN and DONALD C. HARRISON

Tested successfully in eight patients, this improved coronary sinus catheter facilitates catheterization of the great cardiac vein and allows regional determinations of both cardiac venous flow and metabolism using a single catheter. No episodes of perforation, tamponade or serious cardiac arrhythmias resulted from its use.

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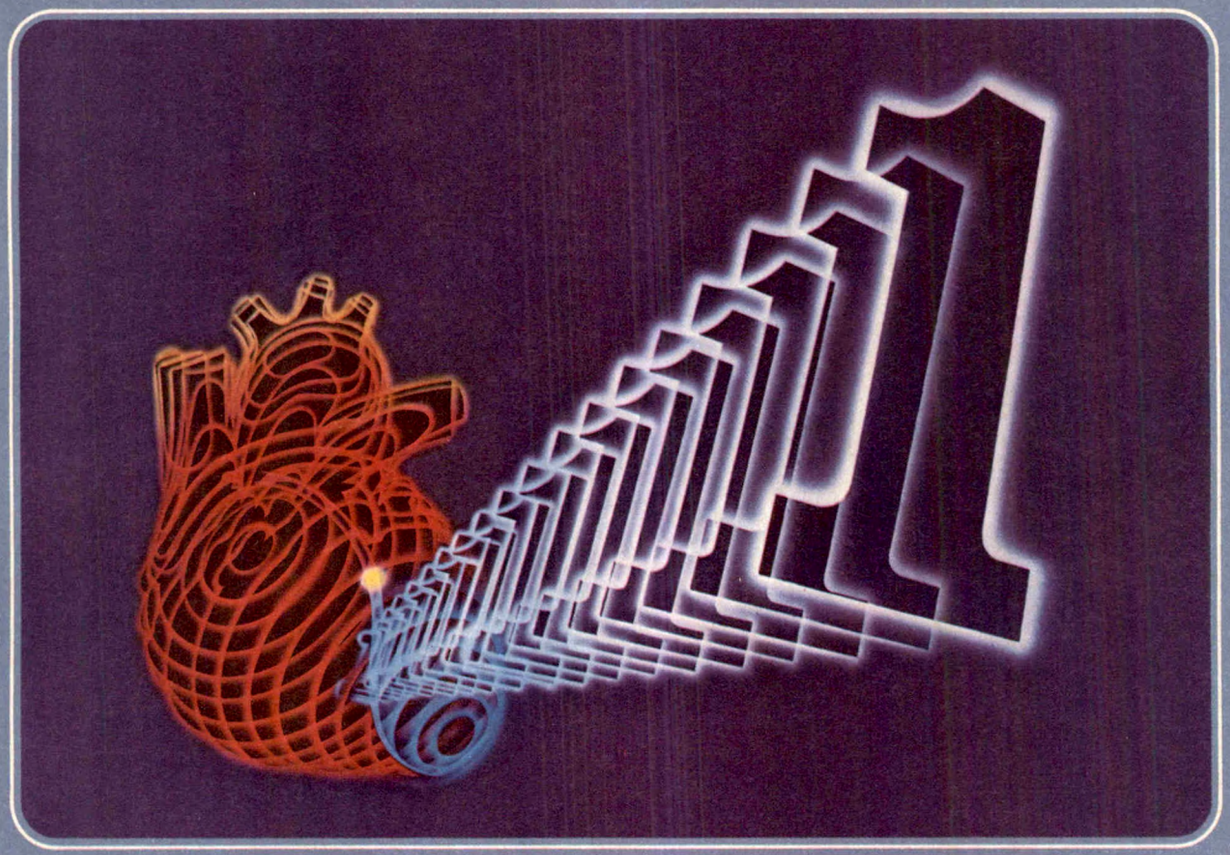
1001 Management of Aortic Arch Interruption With Prostaglandin E_1 Infusions and Microporous Expanded Polytetrafluoroethylene Grafts

KENNETH G. ZAHKA, J. MICHEL A. ROLAND, ANTHONY F. CUTILLETTA, TIMOTHY J. GARDNER, JAMES S. DONAHOO and LANGFORD KIDD

This report describes the management of eight infants, all less than 4 days old, with interruption of the aortic arch. Five of six infants responded dramatically to the administration of prostaglandin E_1 with the return of their limb pulses, abatement of peripheral vasoconstriction and lessening of their metabolic acidosis. Seven of the group subsequently underwent aortic reconstruction with a polytetrafluoroethylene graft which allows for successful shunting of small caliber blood vessels. The combined use of prostaglandin E_1 and polytetrafluoroethy-

continued on page A30

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nadolol tablets

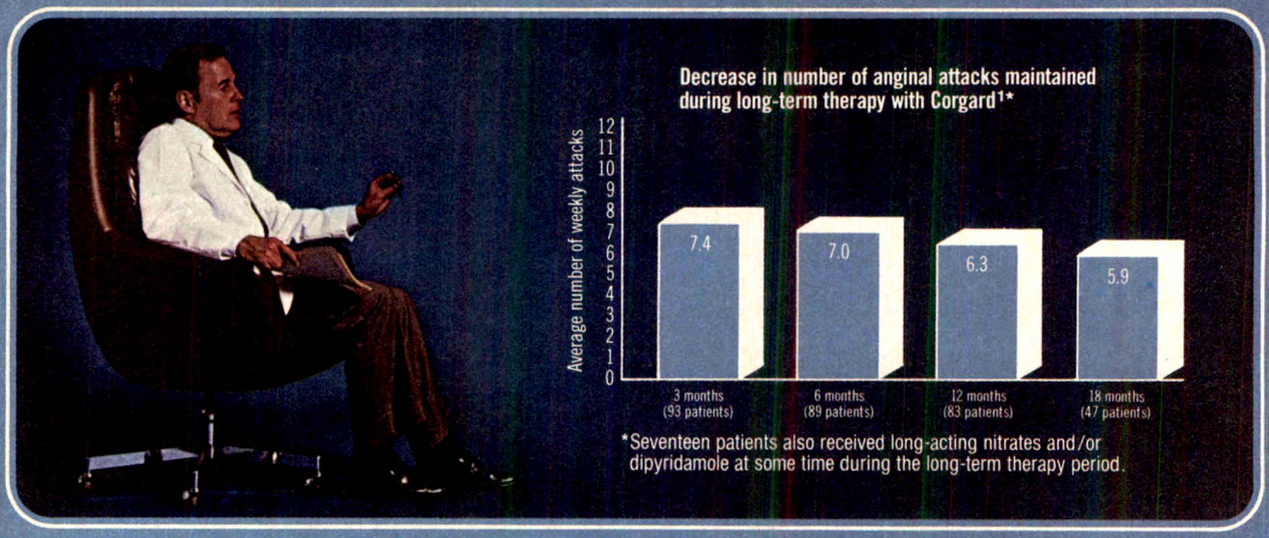


The first and only beta-blocker with once-a-day dosage

In the treatment of angina pectoris

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See last page of this advertisement for brief summary.



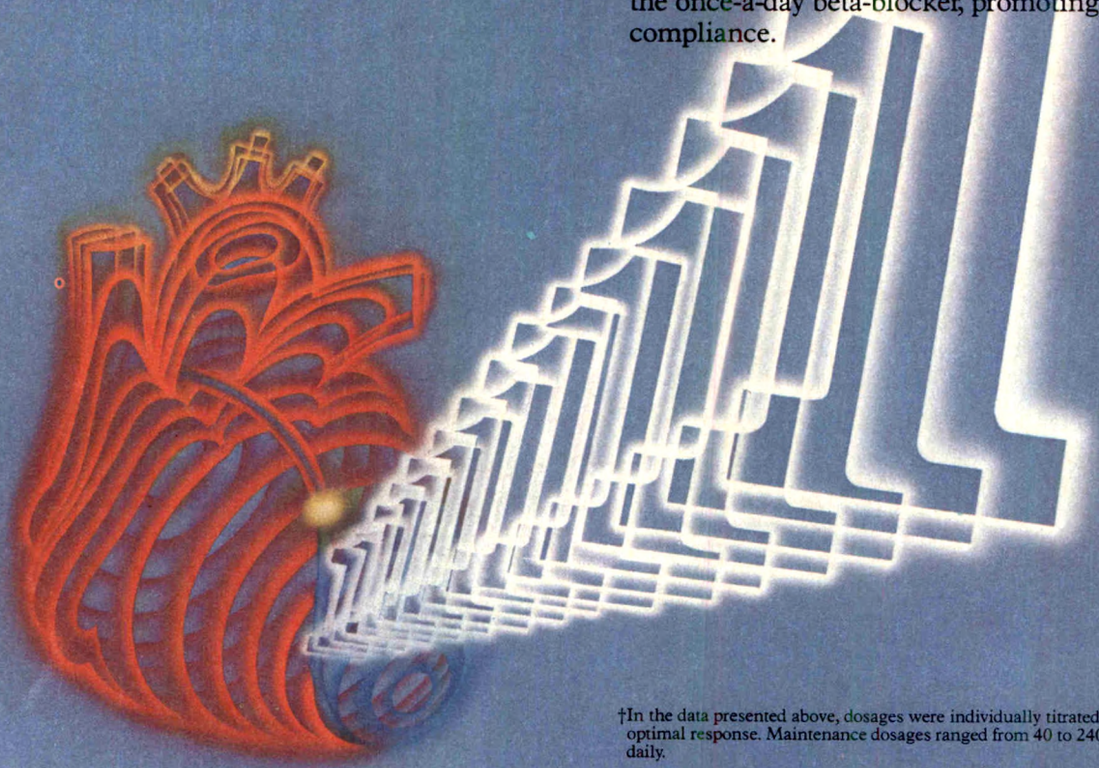
CORGARD® [nadolol tablets]:

Once-a-day, everyday, Corgard offers round-the-clock protection

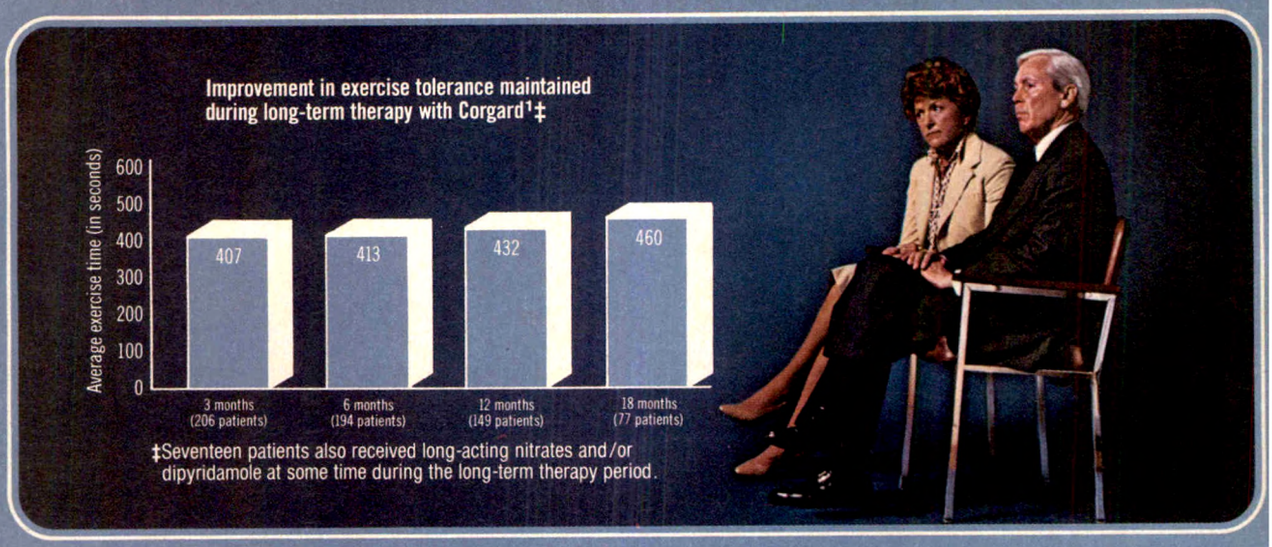
A single daily dose of Corgard offers prophylaxis in angina pectoris, helping to protect the patient all day and all night from painful attacks. And in extended clinical studies, the efficacy of Corgard — as demonstrated by a decreased rate of anginal attacks and an increase in exercise tolerance — was maintained.[1]

Once-a-day, everyday, Corgard decreases the frequency of anginal attacks

Corgard taken just once daily offers round-the-clock protection from angina pain. In one short-term study, Corgard, once a day, decreased the average number of anginal attacks per week in 115 patients with angina, from 13.6 pretherapy to 6.4 at the end of 14 weeks of therapy, a mean decrease of 59%.[1†] In 19% of the 115 patients, anginal attacks were completely eliminated. And the long half-life (20 to 24 hours) makes Corgard the once-a-day beta-blocker, promoting patient compliance.



†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



Effective control of angina pectoris

Once-a-day, everyday, Corgard increases exercise tolerance

Corgard allows the angina patient to do more. In 147 patients in the same short-term study as the one at left, Corgard, once a day, increased ergometry time by 25%, improving exercise tolerance from an average of 365 seconds pretherapy to 427 seconds at the end of 14 weeks of therapy.[1] In 21% of the 147 patients, the end point of exercise was fatigue rather than angina pain. And the single daily dose of Corgard can be taken at the patient's convenience, without regard to meals.

Once-a-day, everyday, Corgard decreases nitroglycerin usage[1]

Corgard blocks catecholamine influence on myocardial activity, decreases myocardial oxygen demand, and does not have a direct myocardial depressant effect.

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nadolol tablets



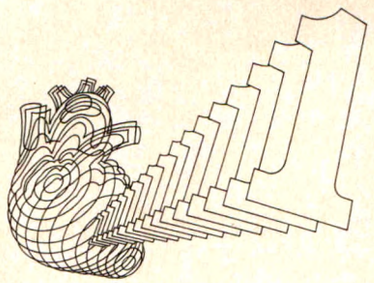
40 mg, 80 mg, and 120 mg tablets

The common-sense beta-blocker for angina pectoris

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See next page for brief summary.

Effective control of angina pectoris... and hypertension



CORGARD® nadolol tablets

40 mg, 80 mg, and 120 mg tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, or 120 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:

1. Data on file, Squibb Institute for Medical Research.

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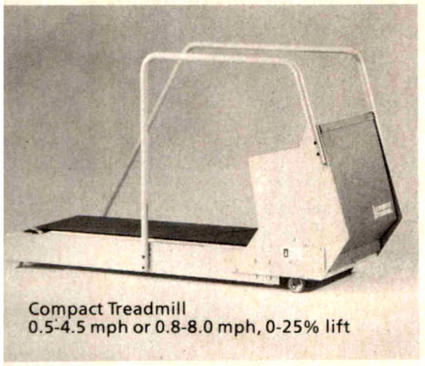
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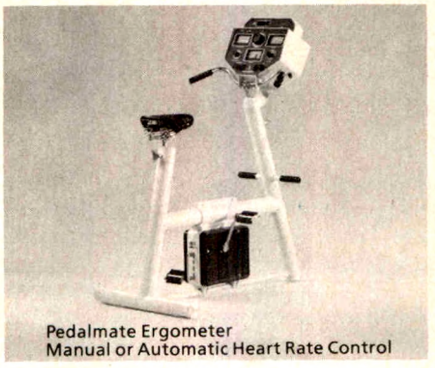
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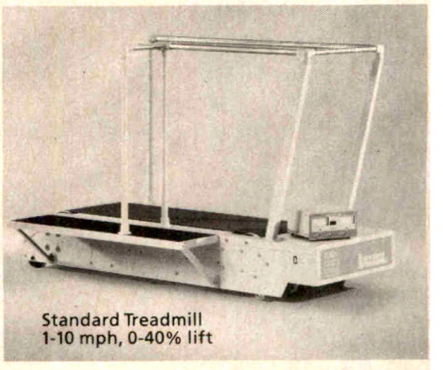
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lene grafts has improved the immediate prognosis for neonates with interruption of the aortic arch, but the long-term mortality rate of 62 percent remains high.

1006 Stress-Induced Ventricular Arrhythmia After Repair of Tetralogy of Fallot

ARTHUR GARSON, Jr., PAUL C. GILLETTE, HOWARD P. GUTGESELL and DAN G. McNAMARA

Treadmill exercise testing with a modified Bruce protocol in 104 patients at a mean age of 13.8 years an average of 7 years after repair of tetralogy of Fallot induced ventricular arrhythmias in 30 percent of the group. Five of 15 patients with arrhythmia at rest had more arrhythmia during exercise. Ventricular arrhythmia during treadmill exercise was related to abnormal hemodynamic status. Since multiform premature ventricular complexes, couplets or ventricular tachycardia with exercise testing are highly associated with abnormal hemodynamic status and sudden death, patients after repair of tetralogy of Fallot should be treated for ventricular antiarrhythmic medication. Patients with good hemodynamic results and single uniform premature ventricular complexes may benefit from the administration of a relatively benign drug such as phenytoin.

1013 Dual Atrioventricular Nodal Pathways: A Benign Finding in Arrhythmia-Free Children With Heart Disease

ALFONSO CASTA, GRACE S. WOLFF, ASHOK V. MEHTA, DOLORES TAMER, OTTO L. GARCIA, ARTHUR S. PICKOFF, PEDOR L. FERRER, RUEY J. SUNG and HENRY GELBAND

Diagnostic cardiac catheterization and electrophysiologic studies in 78 children with associated congenital or acquired heart disease revealed dual A-V nodal pathways in 35 percent of the 51 postoperative subjects. Supraventricular tachycardia was neither induced during electrophysiologic evaluation nor did it develop over a follow-up period of 1 month to 15 years. These observations indicate that dual A-V nodal pathways are common in arrhythmia-free children with heart disease and probably represent functional properties of the human A-V node. The effective and functional refractory periods of the fast A-V nodal pathway ranged between 220 to 570 and 270 to 610 ms, respectively; those of the slow A-V nodal pathway ranged between 240 to 450 and 350 to 665 ms, respectively. The A-V nodal pathway did not differ significantly in patients studied before and after operation.

REPORTS ON THERAPY

1019 Antianginal and Myocardial Metabolic Properties of Verapamil in Coronary Artery Disease

JACK FERLINZ and MARVIN E. TURBOW

In 12 men with significant coronary artery disease studied at rest and during stress with atrial pacing before and after intravenous treatment with verapamil, this drug was found to decrease left ventricular myocardial metabolic demands and greatly increase the threshold to angina. Angina pectoris occurred in all patients stressed with atrial pacing before treatment with verapamil; the mean threshold to pain was 93 ± 67 seconds. After infusion of verapamil, the threshold to pain increased to 191 ± 183 seconds in six patients and the remaining six experienced no pain. In this study the administration of verapamil invariably decreased the coronary blood flow and produced a decrease in the myocardial oxygen consumption that paralleled the decrease in coronary flow. Coronary vascular resistance did not change appreciably.

1027 Efficacy of Diltiazem for Control of Symptoms of Coronary Arterial Spasm

STEVEN J. ROSENTHAL, ROBERT GINSBURG, IRENE H. LAMB, DONALD S. BAIM and JOHN S. SCHROEDER

Diltiazem administered in a prospective randomized double-blind crossover trial to 13 patients with clinical angina attributed to documented coronary arterial spasm proved highly effective in controlling the symptoms of active coronary arterial spasm without side effects and with excellent patient tolerance. In this study 6 of the 13 patients given the lower dosage (120 mg/day) and four patients given the higher dosage (240 mg/day) of diltiazem

continued on page A37



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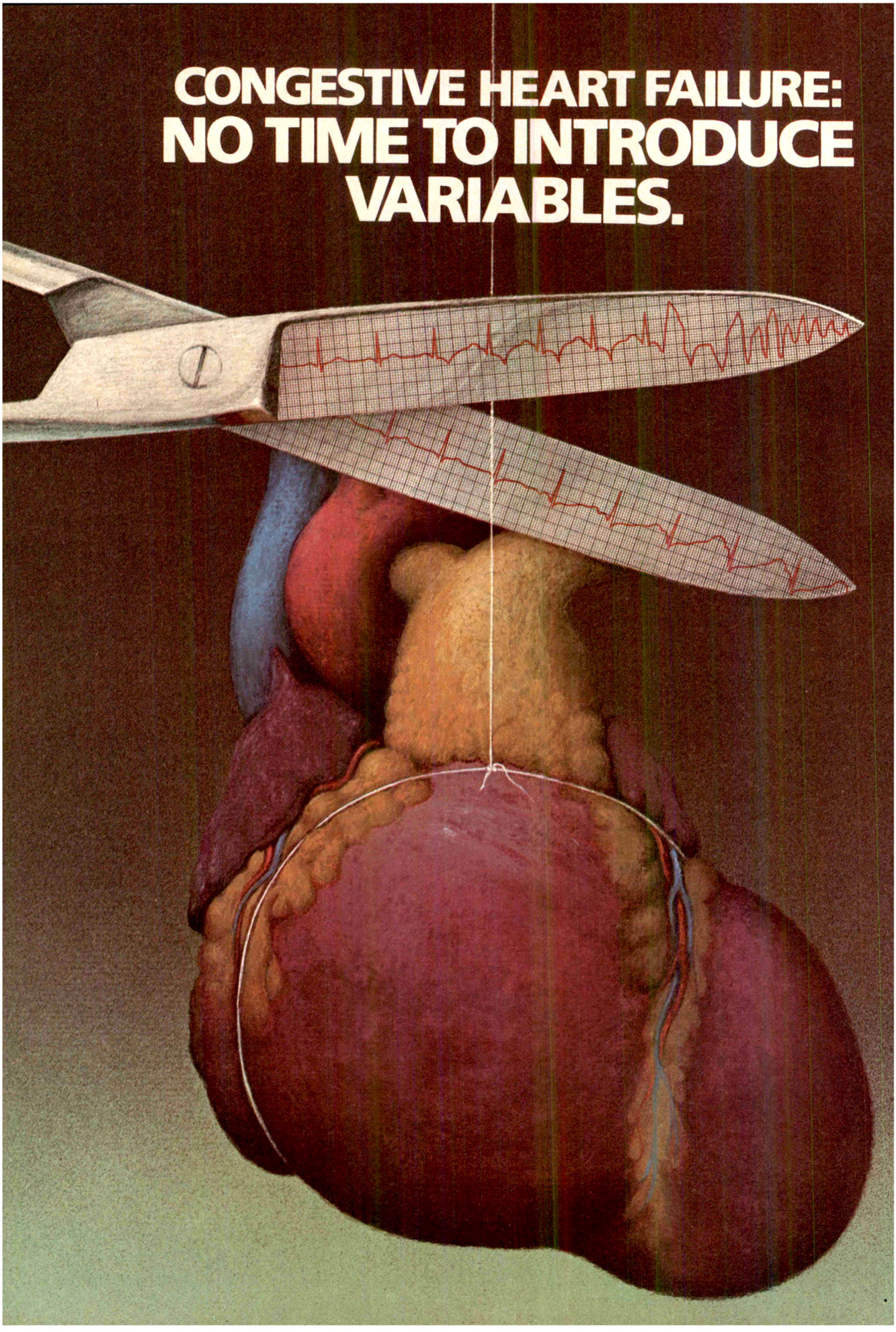
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Both digitalis and diuretics are almost always used in congestive heart failure. But both can cause serious cardiac arrhythmias.[1] *Digitalis, because digitalization is one of the most precarious titrations in all of medicine. And diuretics, because diuretic-induced hypokalemia increases the vulnerability to digitalis toxicity.*[2] *See warnings and precautions in the brief summary of product information on the next page.*

In serious congestive heart failure, the diuretic most frequently administered with digitalis is LASIX® brand of furosemide. However, the bioavailability of furosemide may be significantly altered by a change in tablet disintegrants and/or excipients.[3,4,5] And variations in the bioavailability of unlawfully-marketed furosemide tablets have produced unpredictable and serious clinical effects.[6]

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Before prescribing, please consult complete product information, a summary of which appears on the following page.

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References: 1. Moe GK, Farah AE: Digitalis and allied cardiac glycosides, in Goodman LS and Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1970, pp 653-682. 2. Smith TW: Digitalis: Ions, inotropy and toxicity, editorial. *N. Engl. J. Med. 299*:545, 1978. 3. Rubinstein MH, Eastwood BA, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: The effect of lubricant type and concentration on the bioavailability of furosemide from 80 mg tablets: *J. Pharm. Pharmacol. 30* (suppl.):12P, Dec. 1978. 4. Rubinstein MH, Price EF, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: In vivo evaluation of the effect of five disintegrants on the bioavailability of furosemide from 40 mg tablets: *J. Pharm. Pharmacol. 29* (Suppl.):5P, Dec. 1977. 5. Rubinstein MH, Rughani JM, School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.: The effect of four tablet binders on the bioavailability of furosemide from 40 mg tablets: *Drug Development and Industrial Pharmacy* 4(6): 541-553 (1978). 6. HEW News, publication 79-6, U.S. Department of Health, Education and Welfare (Food and Drug Administration), March 30, 1979, pp 2-3.

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Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter; and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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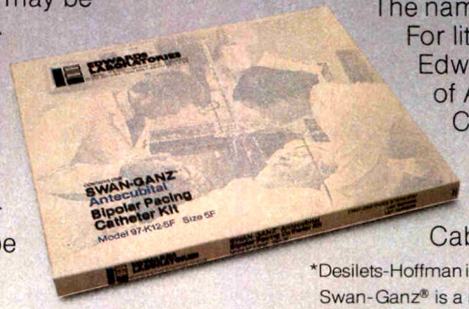
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QUICK QUIZ

Fig. 1

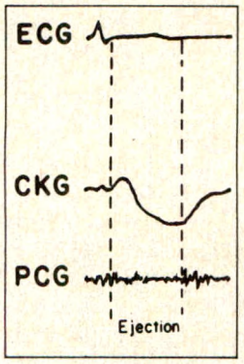


Fig. 2

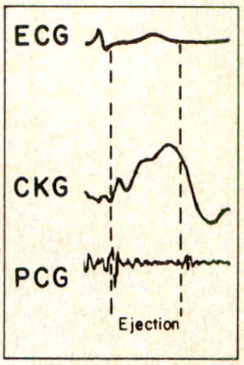


Fig. 3

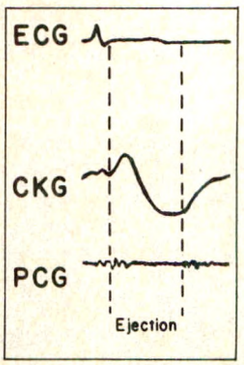
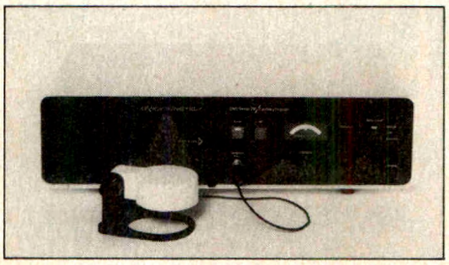


Fig. 4



I. Figure 1 is a pre-stress CKG™ (Cardiokymograph) tracing of the left ventricle (V3 position), it demonstrates:*

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

II. Figure 2 is a two minute post-stress CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

III. Figure 3 is a thirty minute post-stress resting CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

IV. Figures 1, 2 and 3, taken together, demonstrate:

- ☐ A. stress induced ventricular wall motion abnormalities consistent with ischemia
- ☐ B. normal ventricular wall motion

V. According to recently published(1) data, the CKG (Cardiokymograph) stress test is:

- ☐ A. 98% sensitive—98% specific
- ☐ B. 59% sensitive—69% specific
- ☐ C. 74% sensitive—95% specific
- ☐ D. 40% sensitive—60% specific

VI. Figure 4 is a photograph of:

- ☐ A. CKG/700 (Cardiokymograph)
- ☐ B. a noninvasive device that provides an analog representation of wall motion
- ☐ C. a low cost, simple device to be used in conjunction with stress testing to enhance diagnostic accuracy
- ☐ D. all of the above

REFERENCE

(1) Silverberg R A, Diamond G A, Vas R, Tzivoni D, Swan H J C, Forrester J S. Noninvasive Diagnosis of Coronary Artery Disease: The Cardiokymographic Stress Test, Circulation, Vol. 61, No. 3, pgs. 579-589.

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QUICK QUIZ—ANSWERS

I. A. normal systolic inward motion **II.** C. holosystolic outward motion **III.** A. normal systolic inward motion **IV.** A. stress induced ventricular wall motion abnormalities consistent with ischemia **V.** C. 74% sensitive—95% specific **VI.** D. all of the above

had complete resolution of their pain. There was no evidence for a rebound phenomenon secondary to abrupt discontinuation of the drug or a delay in clinical response to the institution of drug therapy.

1033 Modification of Ventricular Tachycardia by Procainamide in Patients With Coronary Artery Disease

TOBY R. ENGEL, STEVEN G. MEISTER and JERRY C. LUCK

In traditional doses of infusion, procainamide prevented the extrastimulus induction of ventricular tachycardia in only 2 of 15 patients with coronary artery disease. Larger doses prevented induction of ventricular tachycardia in 1 of 8 patients. Rapid ventricular rates greater than 210 beats/min that were not slowed 50 percent or more after infusion of 1 g of procainamide predicted failure of this drug to prevent ventricular tachycardia. These data suggest that the dose-response potency of procainamide in further slowing of ventricular tachycardia predicts ultimate prevention of the arrhythmia. Although procainamide was the most effective drug used in this study, it facilitated induction of tachycardia in the majority of patients. The mechanism of successful procainamide action is to slow conduction in a reentrant circuit rather than to prolong refractoriness to a greater extent than the slowing of conduction.

1039 Positive Inotropic Effects of Hydralazine in Human Subjects: Comparison With Prazosin in the Setting of Congestive Heart Failure

CARL V. LEIER, CHRISTOPHER E. DESCH, RAYMOND D. MAGORIEN, DOUGLAS W. TRIFFON, DONALD V. UNVERFERTH, HARISIOS BOUDOULAS and RICHARD P. LEWIS

Unlike first dose prazosin, hydralazine, a vasodilator widely used in the management of chronic congestive failure, significantly shortened the preejection period and increased the $\Delta P/\Delta t$ over 8 hours after the oral administration of 75 or 100 mg to 14 patients with left ventricular dysfunction and congestive heart failure. These data suggest that hydralazine elicits a positive inotropic response in the failing human ventricle which may not be essential for augmentation of cardiovascular performance. First dose prazosin elicited a comparable increase in stroke volume without increasing ventricular inotropy. Both hydralazine and prazosin may not be ideal vasodilators despite their widespread use.

SEMINAR ON CALCIUM CHANNEL BLOCKERS—PART I

1045 Introduction

EUGENE BRAUNWALD

1047 Comparative Pharmacology of Calcium Antagonists: Nifedipine, Verapamil and Diltiazem

PHILIP D. HENRY

This review of calcium antagonists indicates that they constitute a heterogeneous group of agents with dissimilar structural, electrophysiologic and pharmacologic properties. Nifedipine is an efficacious long-acting vasodilator useful in relieving angina caused by coronary vasospasm. Verapamil is the drug of choice for the treatment of reentrant supraventricular arrhythmias but is only moderately effective as an antianginal agent. It probably acts by lengthening the effective and functional refractory periods of the A-V node and prolonging the A-V nodal transmission time. Reversion to sinus rhythm occurs in more than 90 percent of the patients. Diltiazem is useful for the treatment of angiospastic angina. Its value as an antiarrhythmic agent is yet to be clarified. The application of these three drugs to the treatment of cardiac arrhythmias, angina pectoris, arterial hypertension, left ventricular failure and cardiomyopathy is discussed.

1059 Effects of Nifedipine on Electrical Activity of Cardiac Cells

KENNETH H. DANGMAN and BRIAN F. HOFFMAN

Nifedipine concentrations of 20 to 200 μg/liter that will only shorten the plateau of normal action potentials can suppress abnormal automatic activity in canine cardiac Purkinje fibers. These and other observations on its action on electrical activity of normal and abnormal cardiac cells suggest that nifedipine may prove to be a useful antiarrhythmic drug. It should have no major undesirable effects on electrical activity of normal cardiac fibers

continued on page A42

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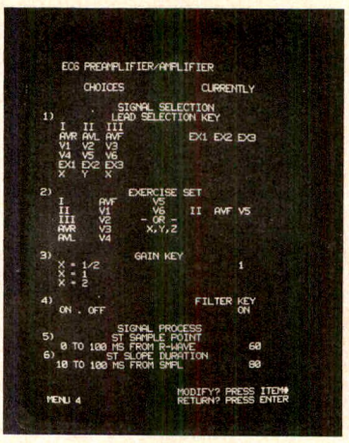
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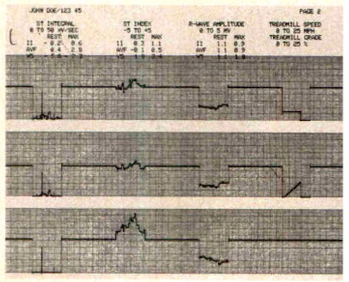
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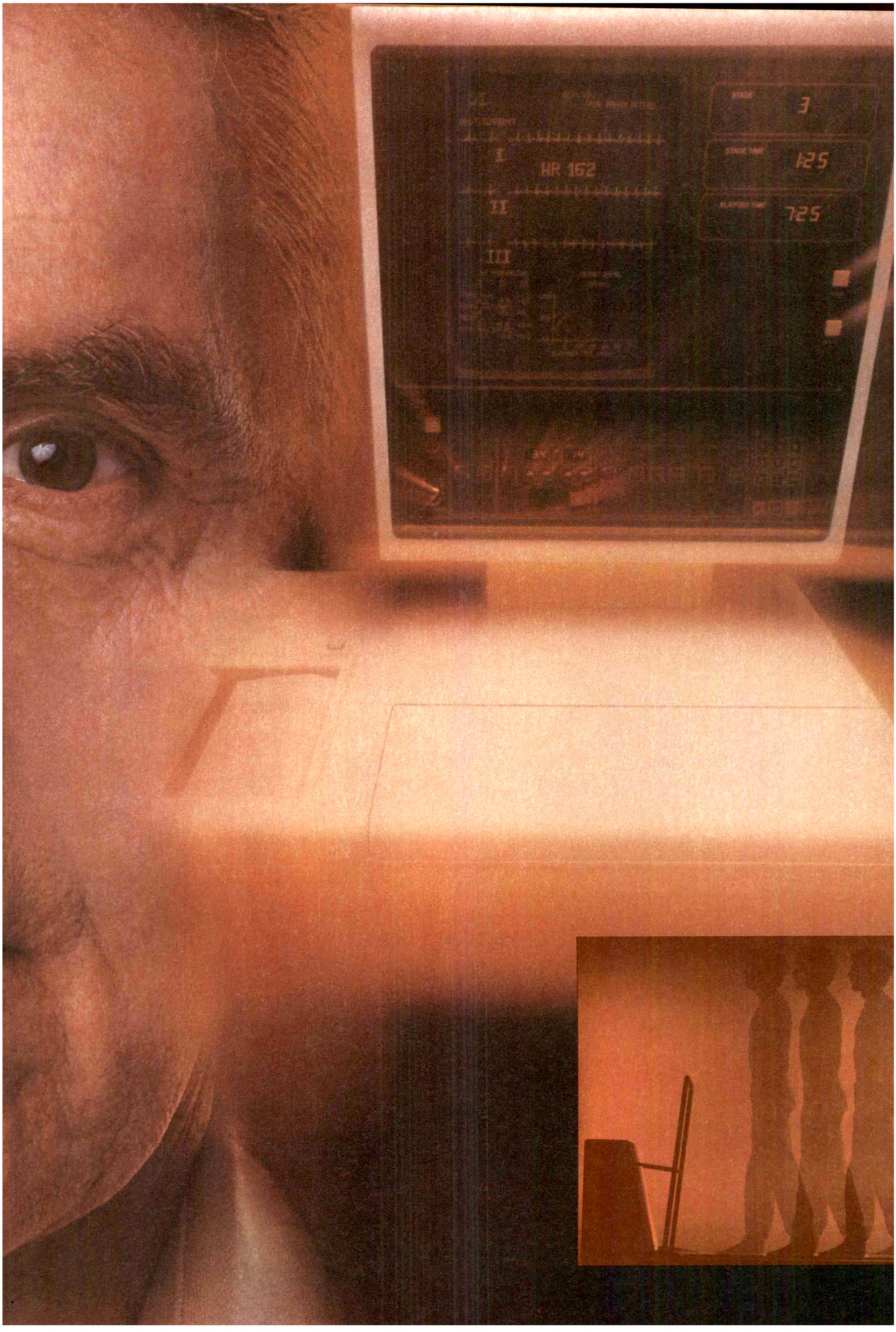
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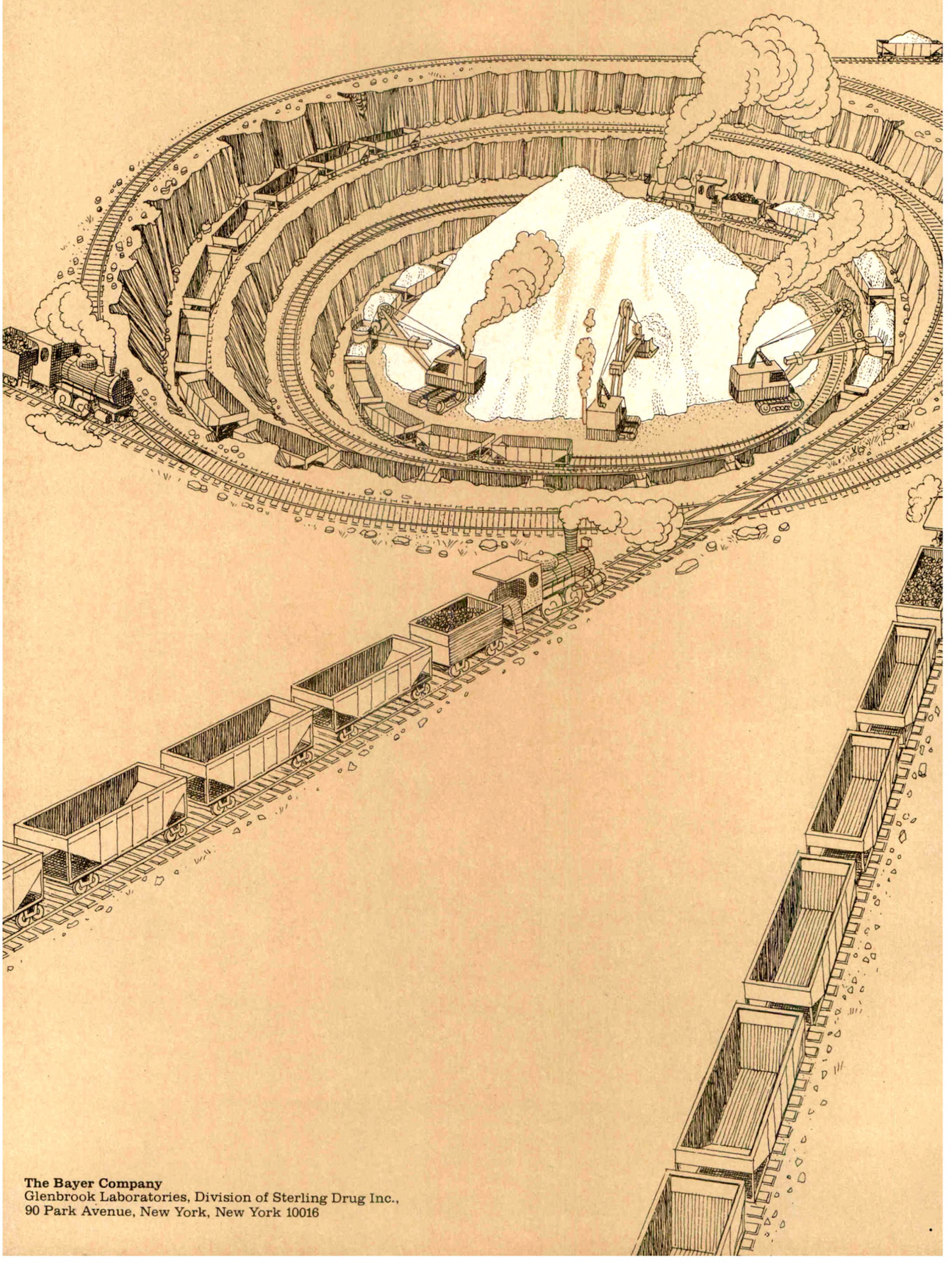
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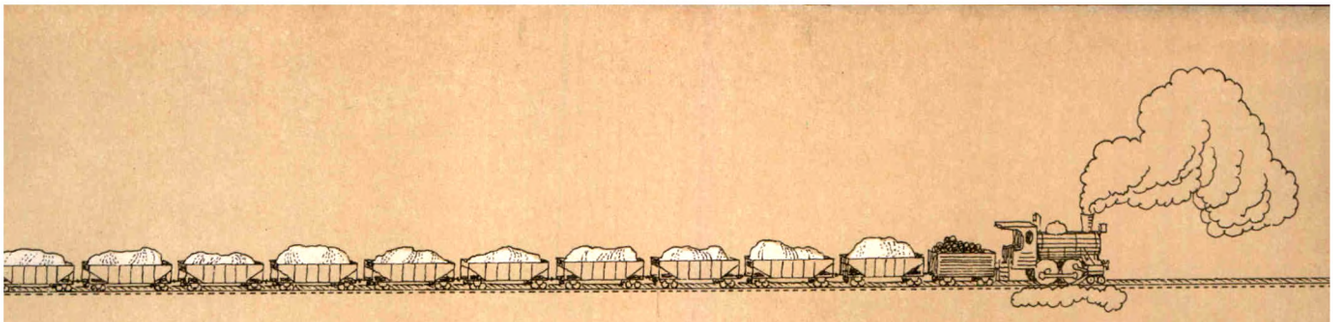
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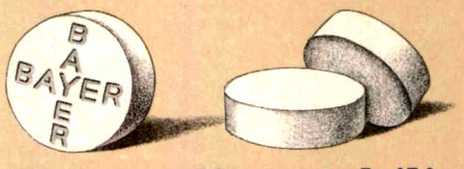
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but should exert a protective effect against arrhythmias caused by several of the mechanisms engendered by ischemia, if sufficiently high tissue concentrations of the drug are achieved.

EDITORIALS

1069 External Pressure Circulatory Assistance: No Light on the Shadow
LESLIE A. KUHN

SPECIAL DEPARTMENTS

1073 Letters to the Editor

1075 American College of Cardiology News

1079 Volume Indexes

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beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness
children have not been established.

Adverse Reactions Most adverse effects ha
been mild and transient.

Central Nervous System: Tiredness and diz
have occurred in about 10 of 100 patients. De
sion was reported in about 5 of 100 patients.
Headache, nightmares, and insomnia have a
been reported but drug relationship is not cle

Cardiovascular: Shortness of breath and
bradycardia have occurred in approximately
100 patients. Cold extremities; arterial insuffic
usually of the Raynaud type; palpitations anc
gestive heart failure have been reported. See
traindications, Warnings, and **Precautions**

Respiratory: Wheezing (bronchospasm) has
reported in less than 1 of 100 patients. See **W**
ings.

Gastrointestinal: Diarrhea has occurred in a
of 100 patients. Nausea, gastric pain, constip
flatulence, and heartburn have been reportec
100 or less.

Allergic: Pruritus has occurred in less than 1
patients.

Miscellaneous: Peyronie's disease has beer
ported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associa
with the beta blocker practolol has not been r
ported with Lopressor during investigational
and foreign marketing experience.

Potential Adverse Effects: In addition, a vari
adverse effects not listed above have been re
ported with other beta-adrenergic blocking a
and should be considered potential adverse
of metoprolol.

Central Nervous System: Reversible mental d
pression progressing to catatonia; visual distu
bances; hallucinations; an acute reversible sy
drome characterized by disorientation for time
place, short-term memory loss, emotional lab
slightly clouded sensorium, and decreased p
formance on neuropsychometrics.

Cardiovascular: Intensification of AV block (se
Contraindications).

Hematologic: Agranulocytosis, nonthrombo-
cytopenic purpura, thrombocytopenic purpur

Allergic: Erythematous rash, fever combined
aching and sore throat, laryngospasm and re
tory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blo
urea levels in patients with severe heart disea
elevated serum transaminase, alkaline phos-
phatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopre
should be individualized. The usual initial dose
50 mg twice daily whether used alone or adde
diuretic. The dosage may be increased at wee
(or longer) intervals until optimum blood press
reduction is achieved. In general, the maximu
fect of any given dosage level will be apparent
one week of therapy. Usual maintenance dosa
approximately 100 mg twice a day, with a rang
100 to 450 mg per day. Dosages above 450 m
day have not been studied. While twice-daily
ing is effective and can maintain a reduction in
blood pressure throughout the day, some patie
especially when lower dosages are used, will e
rience a modest rise in blood pressure toward
end of the 12-hour dosing interval. This can be
evaluated by measuring blood pressure near t
end of the dosing interval to determine whethe
satisfactory control is being maintained throug
the day. If control is not adequate, a larger dos
three times daily therapy, may achieve better c
trol. Beta$_1$ selectivity diminishes as dosage of
Lopressor is increased.

This drug should be stored at controlled room
perature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shap
scored, light red, film-coated) and 100 mg
(capsule-shaped, scored, light blue, film-coate
are supplied in bottles of 100 and 1,000 and Ur
Dose Packages of 100.

Store at controlled room temperature and prote
from moisture.

Dispense in tight, light-resistant container (USI

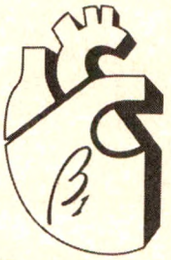
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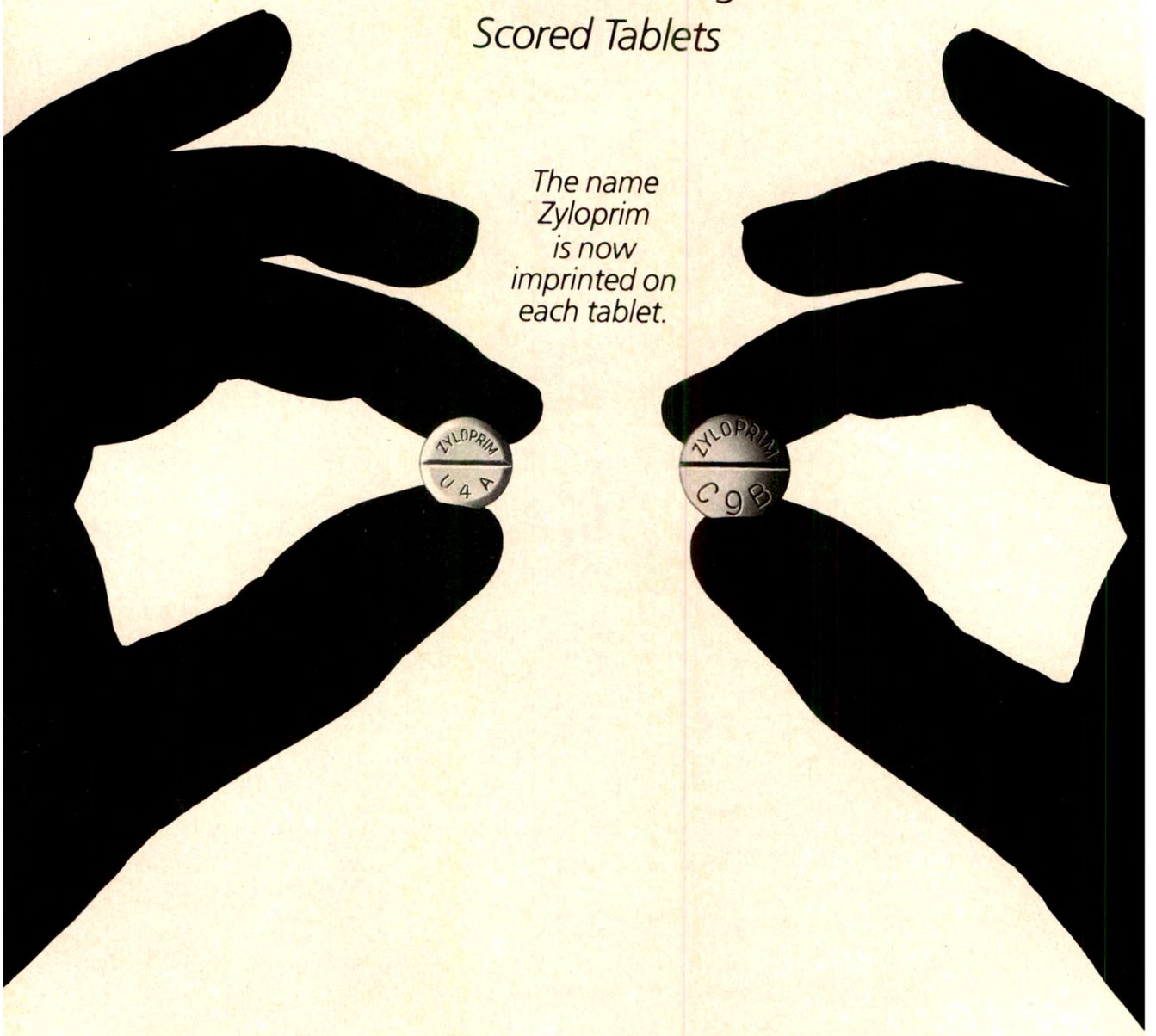
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CLINICAL STUDIES

Exercise Testing Early After Myocardial Infarction: Predictive Value for Subsequent Unstable Angina and Death

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Recently, modified treadmill exercise testing before hospital discharge has been reported to be safe in patients after uncomplicated myocardial infarction. Accordingly, the frequency of treadmill exercise-induced abnormalities and their prognostic value were evaluated in 130 patients with uncomplicated myocardial infarction. Seventy-eight patients (60 percent) had one or more treadmill exercise-induced abnormalities; 42 had S-T segment depression, 35 had angina and 17 had an inadequate blood pressure response. During the mean follow-up period of 11 months, 27 patients experienced unstable angina, 12 had a recurrent myocardial infarction and 10 died of cardiac causes. Compared with patients with no exercise-induced abnormality, patients with S-T segment depression, angina pectoris or an inadequate blood pressure response had a significantly greater ($p < 0.001$) incidence of all cardiac events during the follow-up period. Furthermore, unstable angina pectoris was significantly more frequent ($p < 0.005$) in patients with S-T segment depression or angina pectoris. Finally, when the patients with ischemic treadmill abnormalities were combined with the patients exhibiting an inadequate blood pressure response, they had a statistically greater ($p < 0.005$) incidence of cardiac death than that of patients with no treadmill abnormalities. Therefore, these three abnormalities during modified treadmill exercise testing before hospital discharge identify patients with uncomplicated myocardial infarction who are at risk for a future cardiac event.

Uncomplicated myocardial infarction is often the harbinger of future cardiac events such as unstable angina pectoris, recurrent myocardial infarction or death. This is particularly true within the first 6 months after infarction.[1] Recently, the feasibility and safety of modified treadmill exercise testing before hospital discharge after an uncomplicated myocardial infarction have been established.[2–10] In addition, the development of certain abnormalities during modified treadmill exercise testing has been reported to predict future cardiac events.[6–10] Specifically, S-T segment depression during such testing has been shown to predict cardiac death after myocardial infarction.[6–8,10] Furthermore, S-T depression and angina pectoris have predicted stable exertional angina after infarction.[9] However, little information is available con-

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cerning the prognostic value of these treadmill abnormalities for the development of unstable angina pectoris. Also, the frequency and prognostic value of an inadequate blood pressure response during treadmill testing early after myocardial infarction are unknown.

To delineate further the potential value of this noninvasive technique for predicting future cardiac events, we evaluated patients with uncomplicated myocardial infarction with modified treadmill exercise testing before hospital discharge to determine: (1) the frequency of S-T segment depression, angina pectoris, inadequate blood pressure response, and ventricular arrhythmias, and (2) the ability of these treadmill-induced abnormalities to predict unstable angina pectoris, recurrent myocardial infarction and cardiac death.

Methods

Patients: One hundred thirty patients with acute myocardial infarction were evaluated. There were 114 men and 16 women, ranging in age from 24 to 79 years (mean 54). Thirty-one patients (24 percent) had had a prior myocardial infarction. All patients fulfilled the following diagnostic criteria for acute infarction: (1) retrosternal chest pain consistent with myocardial ischemia lasting at least 30 minutes (2) an evolutionary serum enzyme pattern consistent with myocardial necrosis including an elevation of the creatine kinase MB isoenzyme fraction, and (3) electrocardiographic changes. The diagnostic electrocardiographic changes of transmural myocardial infarction included S-T segment elevation, T wave inversion and development of Q waves of at least 40 ms duration and 25 percent or greater of the R wave amplitude in the same lead.[11–13] The electrocardiographic criteria for subendocardial myocardial infarction consisted of S-T segment depression or T wave inversion persisting for at least 24 hours without development of pathologic Q waves.[13,14] These criteria documented an anterior transmural infarction in 44 patients (34 percent), an inferior transmural infarction in 48 patients (37 percent) and a subendocardial infarction in 38 patients (29 percent).

All patients fulfilling the criteria for myocardial infarction were considered potential candidates for the study. However, some patients (approximately 30 percent) were excluded because they described angina pectoris at rest or during in-hospital ambulation for the preceding 5 days, had left ventricular failure on physical examination, had uncontrolled ventricular premature complexes, had hypertension (blood pressure greater than 165/100 mm Hg), or had a physical or mental handicap that precluded cooperation with exercise testing. All patients gave written informed consent for treadmill testing. At the time of treadmill exercise testing, 55 (42 percent) of the 130 patients were being treated with one or more of the following medications: digoxin, 34 patients (26 percent); propranolol, 21 patients (16 percent); quinidine, 22 patients (17 percent); and an antihypertensive drug, 7 patients (5 percent).

TABLE I
Modified Naughton Treadmill Exercise Protocol

	Time (min)							
	0	3	6	9	12	15	18	21
Speed (miles/h)	2	2	2	2	2	3	3	3
Percent grade	3.5	7	10.5	14	17.5	12.5	15	17.5
METS	3	4	5	6	7	8	9	10

METS = multiples of resting energy expenditure.

Treadmill exercise protocol: The study patients performed treadmill exercise testing before hospital discharge, from 7 to 24 days (mean 15) after myocardial infarction. All of these patients had continuous electrocardiographic monitoring of precordial lead V_1, and recordings of precordial leads V_1, V_5 and V_6 during exercise. The exercise protocol described by Naughton et al.[15] with certain modifications was followed (Table I). Blood pressure, determined with cuff sphygmomanometer, and electrocardiographic recordings were obtained in the sitting and standing positions, after 30 seconds of hyperventilation, for each minute of exercise and for a minimum of 6 minutes after exercise or until the heart rate was less than 100 beats/min and the electrocardiogram had returned to baseline. The treadmill exercise evaluation was terminated when the following occurred: heart rate of 130 beats/min, fatigue or dyspnea, angina pectoris, ventricular tachycardia (defined as three or more consecutive ventricular premature complexes), a decrease from peak systolic blood pressure of 20 mm Hg or greater with continued exercise, or a hypertensive blood pressure response (defined as a systolic blood pressure of 200 mm Hg or greater[16] or a diastolic blood pressure of 110 mm Hg or greater). S-T segment depression alone was not a sufficient criterion for terminating the exercise protocol. All patients performed the exercise test without complications.

Data evaluated: The frequency of the following exercise-induced abnormalities was assessed: (1) horizontal or downsloping S-T segment depression on three successive beats of 0.1 mV or more for 0.08 second after the J point from either the isoelectric S-T segment or from the resting level of an S-T segment abnormality [17,18]; (2) angina pectoris; (3) evidence for an inadequate blood pressure response manifested by an increase of 10 mm Hg or less in systolic blood pressure with a peak systolic pressure of 140 mm Hg or less,[16,19] or a decrease of 20 mm Hg or greater in systolic blood pressure from peak systolic pressure with continued exercise[19–21]; and (4) ventricular premature complexes at a rate of 5 or more/min; or ventricular tachycardia.

In 123 (95 percent) of the 130 patients who performed modified treadmill exercise testing, regular follow-up visits were accomplished for at least 6 months (range 6 to 20). Seven patients were lost to follow-up study. We specifically attempted to determine the incidence of unstable angina pectoris, recurrent myocardial infarction and cardiac death. Patients were considered to have unstable angina pectoris only if they were admitted to the hospital for angina of increasing frequency and duration, angina at rest or prolonged bouts of substernal chest pain suggesting myocardial ischemia. The diagnosis of recurrent myocardial infarction was established as previously described. Cardiac deaths were either sudden (occurring within 1 hour after the onset of symptoms) or were associated with other cardiac events for which the patient had been hospitalized for management. For analytic purposes, in each patient only one complication, the most severe, was tabulated.

Statistics: Data analysis was performed with Student's *t* test for nonpaired data, the chi-square test with Yate's continuity correction or the Fischer's Exact test for the comparison of two proportions.[22] Because repeated tests were performed to identify differences and to determine the predictive value of a specific treadmill exercise-induced abnormality compared with findings in the group with no abnormality, the statistical limits of significance were adjusted to avoid a type

I error.[23] Therefore, for these comparisons, it was determined that a value of $p < 0.01$ would denote significance.

Results

Treadmill exercise-induced abnormalities: Of the 130 patients evaluated, 78 (60 percent) had one or more abnormalities during exercise testing (Fig. 1): 42 patients (32 percent) had S-T segment depression, 35 (27 percent) had angina pectoris, 17 (13 percent) had an inadequate blood pressure response to exercise and 20 (15 percent) had ventricular arrhythmia (one had ventricular tachycardia). Fifty-two patients (40 percent) had no detectable exercise-induced abnormality. There were 29 patients (22 percent) among the total of 130 patients studied who had two or more exercise-induced abnormalities, and 7 patients had three simultaneous abnormalities. Seventeen patients had both S-T segment depression and angina pectoris. Therefore, in our study group 60 patients (46 percent) had either S-T segment depression or angina pectoris during treadmill exercise testing before hospital discharge.

Duration of treadmill exercise: The duration of treadmill exercise in the patients with no treadmill exercise-induced abnormality was 11.0 ± 5.4 minutes (± 1 standard devation). Patients with S-T segment depression, angina pectoris or an inadequate blood pressure response had a significantly shorter ($p < 0.001$) exercise duration (7.6 ± 4.2, 7.4 ± 3.6 and 5.2 ± 2.6 minutes, respectively).

Follow-up data: During the 6 to 20 month (mean 11) follow-up period, 27 patients (21 percent) experienced unstable angina pectoris, 12 (9 percent) had recurrent myocardial infarction and 10 (8 percent) died a cardiac death. Of the latter 10 patients, 7 died suddenly and 3 died during hospitalization, (2 during treatment of unstable angina pectoris and left ventricular failure and 1 after a recurrent myocardial infarction complicated by cardiogenic shock). When patients were grouped and analyzed according to transmural versus subendocardial infarction, there were no differences in the overall incidence of all cardiac events or specific type of event during the follow-up period.

The distribution of all future cardiac events for each treadmill exercise-induced abnormality is depicted in Figure 2. Seven of 48 patients in the group with no abnormality had a cardiac event during the follow-up period. By comparison, a significantly greater incidence of future cardiac events was identified in patients with S-T segment depression (24 of 40 patients, chi-square = 17.1, $p < 0.001$), angina pectoris (22 of 34 patients, chi-square = 21.75, $p < 0.001$) and an inadequate blood pressure response to exercise (11 of 17 patients, $p < 0.001$). Furthermore, when patients treated with digoxin were excluded from the group with S-T segment depression, the incidence of future cardiac events remained statistically higher (14 of 28 patients, chi-square = 11.0, $p < 0.001$) than in the group with no abnormality.

The incidence of unstable angina pectoris, recurrent myocardial infarction and cardiac death for each treadmill exercise abnormality was analyzed further (Fig. 3). Four of 48 patients in the group with no abnormality had unstable angina pectoris in the follow-up period. By comparison, unstable angina pectoris occurred significantly more frequently in the group with S-T segment depression (14 of 40 patients, chi-square = 8.27, $p < 0.005$) and the group with angina pectoris (13 of 34 patients, chi-square = 9.08, $p < 0.005$). Furthermore, the incidence of unstable angina pectoris during the follow-up period was significantly more frequent in the total group of patients with S-T segment depression and angina during treadmill exercise than in patients without these descriptors of myocardial ischemia (chi-square = 8.78, $p < 0.005$).

Recurrent myocardial infarction and cardiac death were infrequent during the follow-up period and were

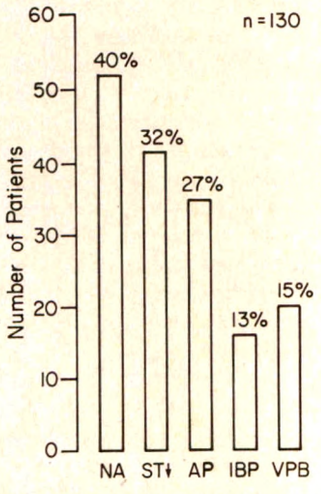


FIGURE 1. Frequency of all treadmill exercise-induced abnormalities for our study group shown as an absolute number of patients and as a percent of the total group of 130 patients (n). AP = angina pectoris; IBP = inadequate blood pressure; NA = no abnormality; ST↓ = S-T segment depression; VPB = ventricular premature beats.

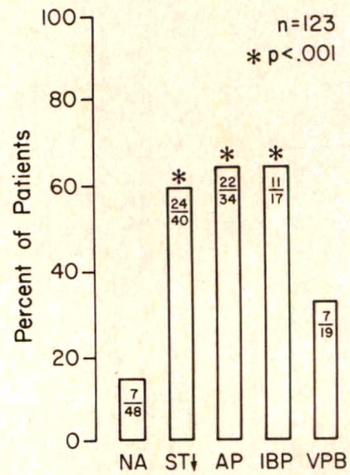


FIGURE 2. Distribution of all future cardiac events for each treadmill response is shown as the percent of patients in each group with completed follow-up. n = total population with completed follow-up; other abbreviations as in Figure 1.

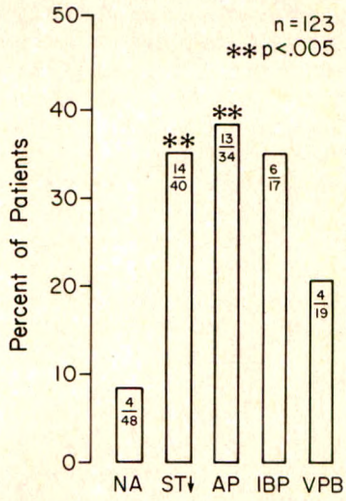


FIGURE 3. Distribution of unstable angina pectoris in each treadmill response group. Format as in Figure 2.

not significantly greater in any group with a specific treadmill exercise-induced abnormality than in the group with no abnormality (Fig. 4). However, cardiac death occurred only in patients with a treadmill exercise-induced abnormality. Furthermore, the two patients with ventricular arrhythmia who died also exhibited either S-T segment depression or an inadequate blood pressure response at the time of treadmill exercise testing. Therefore, when the patients with S-T depression and angina pectoris were combined into one group indicating myocardial ischemia and compared with the group with no abnormality, these abnormalities predicted a greater incidence of cardiac death during the follow-up period ($p < 0.01$). Moreover, when patients with either or both of these two manifestations of myocardial ischemia and an inadequate blood pressure

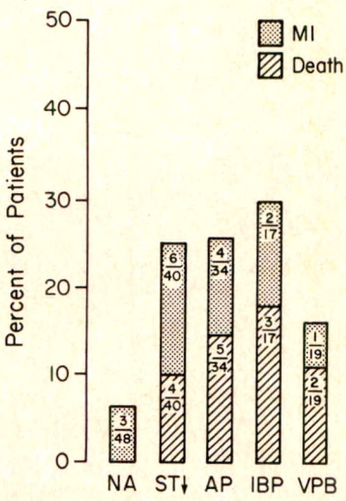


FIGURE 4. Distribution of recurrent myocardial infarction (MI) and cardiac death in each treadmill response group.

response to exercise were grouped together and compared with patients with no treadmill abnormality, the three abnormalities yielded an even higher statistical prediction of cardiac death ($p < 0.005$).

Discussion

Predictions of Recurrent Cardiac Events After Myocardial Infarction

Our data indicate that patients who demonstrate S-T segment depression or angina pectoris during modified treadmill exercise testing before hospital discharge have a significantly greater incidence of future cardiac events, principally unstable angina pectoris, during a 6 to 20 month period after myocardial infarction when compared with patients who have no treadmill abnormality. These ischemic changes did not predict recurrent myocardial infarction, but patients exhibiting these abnormalities had a significantly greater incidence of future cardiac death than did patients with no treadmill abnormality. Moreover, these patients had a significantly reduced exercise tolerance compared with patients with no treadmill abnormality.

S-T depression and angina pectoris during exercise testing: S-T segment depression and angina pectoris, particularly when produced at low levels of energy expenditure on standard treadmill exercise testing, have been demonstrated to have a poor prognosis.[24–26] Initial reports[6] on modified treadmill exercise testing after myocardial infarction also suggested that S-T segment depression might predict future cardiac events. These initial observations were later extended to demonstrate the predictive value of 0.2 mV or greater S-T segment depression, angina and a low maximal work load (less than 4 METS) for future cardiac events.[7,8] In addition, Theroux et al.[10] demonstrated the prognostic value of 0.1 mV or greater S-T segment depression for future cardiac death. Notably, no patient with only angina during modified treadmill exercise testing died in the follow-up period of their study. Moreover, Waters et al.[9] reported that a modified treadmill exercise test performed before hospital discharge that demonstrated S-T segment depression or angina together with a prior history of angina had predictive value for stable angina after myocardial infarction. Our study is consistent with these reports identifying the predictive value of S-T segment depression and angina pectoris at low levels of energy expenditure for future cardiac events including cardiac death. Moreover, we have also demonstrated the value of S-T segment depression and angina during the predischarge modified treadmill exercise test for predicting future unstable angina pectoris.

Inadequate blood pressure response to exercise: Our data also indicate that an inadequate blood pressure response during modified treadmill exercise testing is predictive of future cardiac events. When this hemodynamic abnormality was combined with the ischemic treadmill response, a high predictive value for future cardiac death was demonstrated. Also, patients with these findings exhibited a significantly reduced exercise tolerance compared with that of patients with

no treadmill abnormality. Several authors[20,21] have suggested that a decrease in systolic blood pressure of 10 mm Hg or greater from peak pressure during standard treadmill exercise testing is probably precipitated by myocardial ischemia. In fact, all five of our patients with a decrease of 20 mm Hg or greater in systolic blood pressure had S-T segment depression or angina, suggesting that this may also be an indication of ischemia in postmyocardial infarction patients. Five of our 17 patients with an inadequate blood pressure response were being treated with a medication (propranolol or antihypertensive agent) that could have produced a blood pressure abnormality; therefore, the significance of the abnormality is not clear in these patients. However, even when these five patients were excluded, the predictive value of an inadequate blood pressure response for future cardiac events was not decreased ($p < 0.005$).

Ventricular arrhythmia during exercise: We found no evidence that ventricular premature complexes during modified treadmill exercise testing were of value in predicting future cardiac events. Some authors[10] have suggested that such findings during exercise testing in patients after myocardial infarction may predict sudden cardiac death, others[8] have not found ventricular arrhythmias of value in predicting cardiac events. Our exclusion of patients with uncontrolled arrhythmias detected by other means and the prevalence of antiarrhythmic therapy in our patients may explain the lack of predictive value of ventricular arrhythmias in our study. In addition, the low frequency of ventricular premature complexes in postmyocardial infarction patients performing modified treadmill exercise testing may reflect our exclusion of patients with appreciable left ventricular dysfunction in whom such arrhythmias are more common.[27]

Comparison With Other Reported Studies

Subendocardial versus transmural infarction: The characteristics of our study population are important to evaluate for comparing our results with those of others. Thirty-eight (29 percent) of our patients had a subendocardial myocardial infarction, which is a greater proportion of patients with nontransmural infarction than that in previous studies.[6–8,10] Some investigators[11–13] have reported that patients with subendocardial and transmural myocardial infarction have similar short and long-term prognoses. However, Madigan et al.,[28] evaluating 50 patients with subendocardial infarction, found a particularly high prevalence of multivessel coronary artery disease and incidence of subsequent symptomatic cardiac events. Moreover, Cannom et al.[14] reported a significantly greater incidence of cardiac death in patients with subendocardial than in those with transmural infarction.

Our patients with subendocardial infarction and transmural infarction were similar in age, sex, historical and electrocardiographic evidence of previous myocardial infarction and prevalence of digoxin and propranolol therapy at the time of treadmill exercise testing. Furthermore, no significant difference in the incidence of all cardiac events or of specific events could be demonstrated after myocardial infarction between these two groups. Therefore, we considered it reasonable to group all our patients together and evaluate the predictive value of their treadmill exercise results.

Role of propranolol and digoxin therapy: Theroux et al.[10] reported that significantly more postmyocardial infarction patients with S-T segment depression were being treated with propranolol and that this group had a significantly greater incidence of cardiac death. However, 40 percent of all their patients were receiving propranolol therapy. By contrast, only 21 (16 percent) of our patients were taking propranolol at the time of modified treadmill exercise testing. Also, 34 (26 percent) of our patients were taking digoxin at the time of treadmill testing. Notably, the incidence of subsequent cardiac events in these two patient groups was similar to that of patients not receiving these drugs. Therefore, it would appear that digoxin and propranolol therapy did not select out high risk subgroups that might affect the results of our study.

Role of multivessel coronary disease: An explanation for the poor prognosis in our patients with S-T segment depression, angina pectoris and an inadequate blood pressure response may be the high prevalence rate of multivessel coronary artery disease among these patients. The angiographic studies of Bruschke et al.[29,30] have shown that patients with multivessel coronary artery disease and decreased left ventricular performance have a greater likelihood of experiencing a future cardiac event. Furthermore, ischemic electrocardiographic changes during standard stress testing have been shown to occur more frequently in patients with multivessel coronary artery disease.[31] Recent angiographic studies[32–35] in postinfarction patients have shown that S-T segment depression and angina pectoris during treadmill exercise testing in the postinfarction period are valuable for predicting multivessel coronary artery disease. Also, an inadequate blood pressure response during standard treadmill stress testing has been reported to occur primarily in men with multivessel or left main coronary artery disease.[19–21] Further angiographic studies will be necessary to confirm these findings for postmyocardial infarction patients.

Clinical implications: Our data indicate that many patients who are studied with modified treadmill exercise testing before hospital discharge after an uncomplicated myocardial infarction will exhibit abnormalities of clinical significance. Patients with evidence of myocardial ischemia or an inadequate blood pressure response to exercise, particularly at low levels of energy expenditure, have a greater incidence of future cardiac events, specifically, unstable angina and cardiac death, when compared with patients with no detectable treadmill abnormality. Therefore, such patients may benefit from closer medical follow-up and further diagnostic and therapeutic interventions designed to alter this poor prognosis. There are clinically important questions to be answered concerning the timing of exercise testing after recovery from myocardial infarction and these are being actively evaluated.

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Noninvasive Identification of a High Risk Subset of Patients With Acute Inferior Myocardial Infarction

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Although S-T segment depression of various degrees is known to occur in the precordial electrocardiogram of patients with acute inferior myocardial infarction its prognostic significance is unknown. Left ventricular ejection fraction and regional wall motion were therefore measured noninvasively with radionuclide ventriculography and related to the electrocardiographic changes within 48 hours of the onset of acute transmural inferior infarction in 44 patients who had had no previous infarction.

The mean ejection fraction of 0.45 ± 0.13 (standard deviation) in Group A (24 patients with greater than 1 mm S-T segment depression in at least two of six precordial leads) was lower ($p < 0.001$) than that (0.63 ± 0.08) in Group B (20 patients with no or less than 1 mm S-T depression in these leads). A depressed ejection fraction (less than 0.54) was present in 76 percent of patients in Group A and in 10 percent of patients in Group B ($p < 0.01$). Total wall motion score, a semiquantitative index of regional wall motion abnormality, was lower in Group A (42 ± 6) than in Group B (54 ± 4) ($p < 0.001$). Severe wall motion abnormalities of remote anteroseptal left ventricular segments were observed in 50 percent of patients in Group A and 15 percent of patients in Group B ($p < 0.05$). The peak serum MB creatine kinase levels were higher in Group A than in Group B (167 ± 92 versus 84 ± 56, $p < 0.001$). Left ventricular failure developed in 50 percent of patients in Group A but did not develop in Group B ($p < 0.001$). Five (19 percent) of 24 patients in Group A died in the hospital (3 from pump failure, 1 from arrhythmia and another from electromechanical dissociation). There were no deaths in Group B.

The overall data indicate that patients with inferior wall infarction who have associated precordial S-T segment depression have greater global and regional left ventricular dysfunction presumably due to associated ischemia or infarction in areas remote from the inferior wall and they have relatively high in-hospital mortality and morbidity rates. Early noninvasive detection of this high risk subset may permit the testing of aggresive modes of therapy designed to limit the extent of myocardial ischemic damage with resultant decrease in mortality and morbidity.

The prognosis in inferior wall myocardial infarction is generally believed to be more favorable than that in anterior or anteroseptal infarction.[1–3] However, there is increasing evidence that inferior infarction is not a discrete homogeneous clinical or anatomic entity. For example, inferiorly located myocardial damage as inferred from the electrocardiogram may be associated with right ventricular[4] or "true" posterior left ventricular wall[5] infarction. These complications would be expected to influence the initial hemodynamic perturbations as well as the overall clinical course of inferior infarction.

Variations also occur in the overall 12 lead electrocardiographic patterns in patients with the diagnosis of acute inferior myocardial infarction. It is known that S-T segment elevation and evolutionary Q wave patterns in leads II, III and aVF may be accompanied by S-T segment

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depression of variable degree in one or more of the anterior chest leads (V_1 to V_6) as well as in leads I and aVL. However, neither the precise nature of such S-T depression in these leads nor their prognostic significance in inferior infarction is known. Many electrocardiographers have considered these changes to represent essentially reciprocal electrical phenomena. In some instances, the S-T depression in precordial leads facing the inferoposterior wall may be related to infarction of the posterior left ventricular wall, which does not always have an unequivocal electrocardiographic diagnosis.[5] It is also possible that such precordial S-T depression accompanying acute inferior myocardial infarction may be evidence not only of posterior wall ischemia or infarction, but also of additional anterior ischemia or subendocardial infarction, an occurrence that is likely to have prognostic significance.

Radionuclide ventriculography is a reliable noninvasive technique to detect contraction patterns as sensitive markers of myocardial ischemic injury.[6] Thus, this technique is well suited for determining the significance of the location and extent of global and regional left ventricular contractile abnormalities in relation to the varying precordial S-T segment deviations and to the prognosis in patients with acute myocardial infarction. This study reports the application of radionuclide ventriculography in 44 consecutive patients with a first acute inferior myocardial infarction in order to determine the implications of concomitant precordial S-T depression with respect to location and severity of abnormalities of regional and global left ventricular function and short-term prognosis.

Methods

Patients: Forty-four patients (34 men, 10 women) with a mean age of 63 years (range 27 to 83) with acute transmural inferior myocardial infarction were studied prospectively. Their pertinent clinical data are shown in Table I. Acute transmural inferior myocardial infarction was diagnosed from a history of prolonged chest pain accompanied by typical S-T segment elevation and development of abnormal Q waves (greater than 0.04 second in duration) in two of three electrocardiographic leads (II, III, aVF) with confirmatory changes in serum levels of MB creatine kinase, glutamic oxaloacetic transaminase and lactic dehydrogenase. Patients with bundle branch block, historical or electrocardiographic evidence, or both, of previous myocardial infarction, and electrocardiographic evidence of left ventricular hypertrophy were excluded. No patient was receiving drugs such as digitalis that are known to alter S-T segments.

The 12 lead electrocardiograms of all patients were reviewed at the time of admission to the coronary care unit and, according to the presence or absence of S-T segment depression greater than 1 mm in at least two of six precordial leads (V_1 to V_6), the patients were categorized into two groups: Group A, 24 patients with precordial S-T depression, and Group B, 20 patients without precordial S-T depression. All patients were evaluated within 48 hours of the onset of symptoms. Table II shows the distribution and the magnitude S-T depression in the precordial leads in patients in Group A. There was no relation between the magnitude of S-T depression in these leads and the magnitude of S-T elevation in the inferior electrocardiographic leads.

Radionuclide ventriculography: Left ventricular ejection fraction and regional wall motion patterns were determined noninvasively with radionuclide ventriculography in all patients. After the intravenous injection of 20 to 25 millicuries of in vitro labeled technetium-99m autologous red blood cells, multiple gated equilibrium cardiac blood pool scintigraphy was performed in 45° left anterior oblique and anterior views using a mobile gamma camera (Ohio Nuclear) equipped with a low energy collimator (Medical Data Systems). Left ventricular ejection fraction was determined semiautomatically

TABLE I

Salient Clinical Characteristics in 44 Patients With First Inferior Myocardial Infarction

	Group A (n = 24)	Group B (n = 20)
Age (yr) (mean and range)	63; 27–80	64; 32–82
Previous infarction	None	None
Time (h) (mean and range)		
From onset of symptoms to admission	7; 1–24	8; 2–24
From onset of admission to radionuclide ventriculography	16; 6–24	20; 6–24
Concomitant S-T segment depression (>1 mm) in at least 2 of 6 precordial leads on admission	Present	Absent
Number of patients with ECG signs of true posterior infarction	5	None

ECG = electrocardiographic.

TABLE II

Distribution and Magnitude of S-T Segment Depression (mm) in the Precordial Electrocardiographic Leads in 24 Patients in Group A

Case	Lead V_1	V_2	V_3	V_4	V_5	V_6
1	0	3	2	1.5	1	2
2	1	3.5	1.5	1	1	0
3	1	2.5	1	1	0	0
4	1	2.5	3.5	5.5	4.5	3.5
5	1.5	2	0.5	0	0	0
6	5	8	8	7	2	4
7	1.5	3	1	0.5	0	0
8	1.5	3.5	4	3	3	1
9	6	1	1.5	2	1.5	1
10	0	2	1.5	1	1	1
11	0	0	1	1.5	1.5	1.5
12	3	6	5	5	3	2
13	1	2	2.5	2	1	0
14	0.5	1.5	2	4	4	4
15	2.5	2.5	3	1	0	0
16	0	1	2	2.5	2	0
17	1.5	4	2	1	0	0
18	0	0.5	1.5	1.5	0	0
19	0.5	2	1.5	2	1.5	1.5
20	0	1.5	1.5	0	0	0
21	0.5	1	1.5	0.5	0.5	0.5
22	1.5	3	3	0	0	0
23	1	3	4	2.5	1	1
24	1	4	4	2	1.5	0

from the background-corrected left ventricular activity-time curve.

For the analysis of left ventricular regional wall motion, scintigraphic data were displayed in a flicker-free endless loop movie format. Left ventricular silhouettes from the left anterior oblique and anterior views were divided arbitrarily into 10 segments (Fig. 1), each of which was assigned a score by two independent observers (D.S.B., J.M.), who had no prior knowledge of the clinical or electrocardiographic status of the patient. There was an excellent agreement between the scoring of the two observers; whenever disagreement occurred, an average score was used. For each patient, the total wall motion score, derived by adding scores of 10 individual segments, was used as a semiquantitative index of the extent of left ventricular regional wall motion abnormality. Inferoposterior left ventricular segments 4, 5, 8 and 9 were categorized as infarct-related segments, segments 1, 2, 6 and 7 as anteroseptal segments and segments 3 and (3) as apical segments. This technique of radionuclide ventriculography has previously been validated in our laboratory[6] as accurate and reproducible for the determination of left ventricular ejection fraction and regional wall motion. Serum MB creatine kinase (MB-CK) levels were determined with column chromatography and expressed as IU/liter.

Statistical analysis: The statistical significances of differences in ejection fractions, wall motion scores and of MB-CK isoenzyme levels were assessed by the unpaired *t* test whereas Fisher's exact test was used to assess differences in the comparative frequency of complications in the two groups. Data are expressed as mean values ± standard deviation.

Results

Of the 44 patients with acute inferior myocardial infarction (Table I), 24 (Group A) had precordial S-T segment depression on admission and 20 (Group B) did not. Typical electrocardiographic patterns from the two groups are shown in Figure 2.

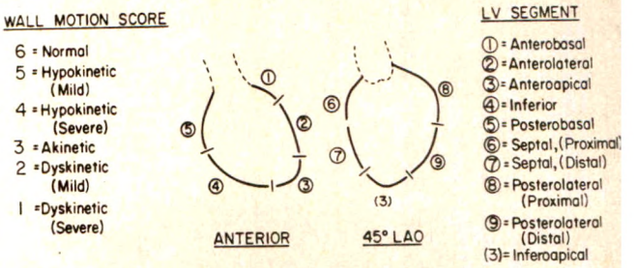


FIGURE 1. Schematic representation of radionuclide left ventriculogram in anterior and 45° left anterior oblique (LAO) views. The left ventricular (LV) silhouette is divided into 10 segments and each segment is given a score depending on the pattern of its wall motion. Inferoposterior segments (4, 5, 8 and 9) are categorized as infarct-related segments and anteroseptal (1, 2, 6 and 7) and apical segments [3 and (3)] as remote noninfarcted segments.

Left ventricular ejection fraction: The differences in left ventricular ejection fraction in the two groups are shown in Figure 3. The value of 0.54 was taken as the lower level of normal on the basis of our previous studies in normal subjects. In 18 (74 percent) of the 24 patients in Group A, the ejection fraction was less than 0.54 and in 4 it was severely depressed (0.30 or less). The mean ejection fraction for the entire Group A was 0.45 ± 0.1 (standard deviation). In contrast, in Group B, no patient had a severely depressed ejection fraction and in only 2 (10 percent) of the 20 patients was the level below 0.5 (Fig. 3). The mean value for ejection fraction in this group was 0.63 ± 0.08, which was significantly (<0.001) different from the corresponding value for Group A.

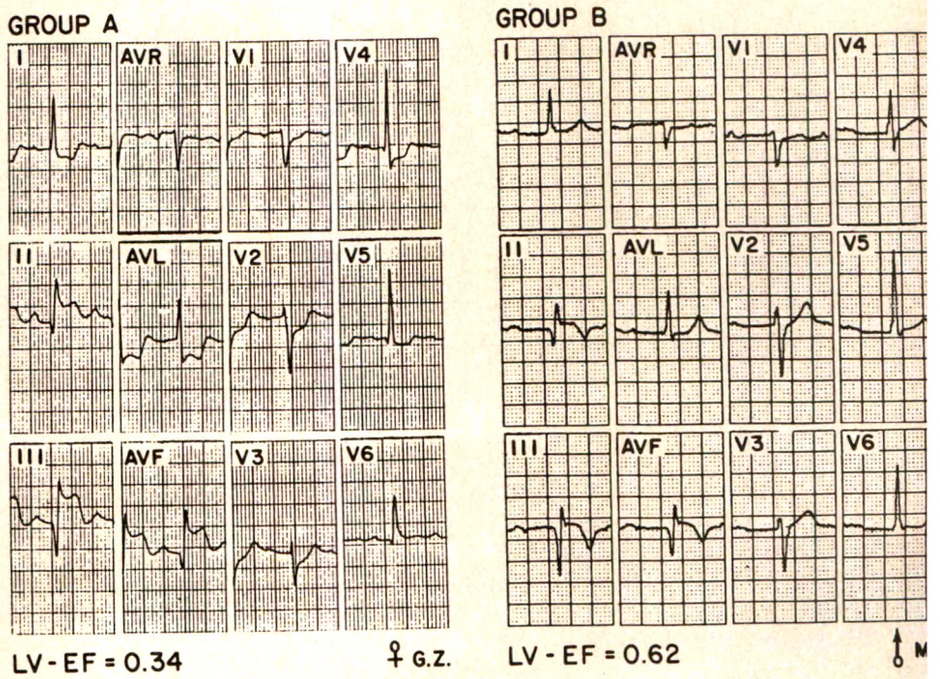
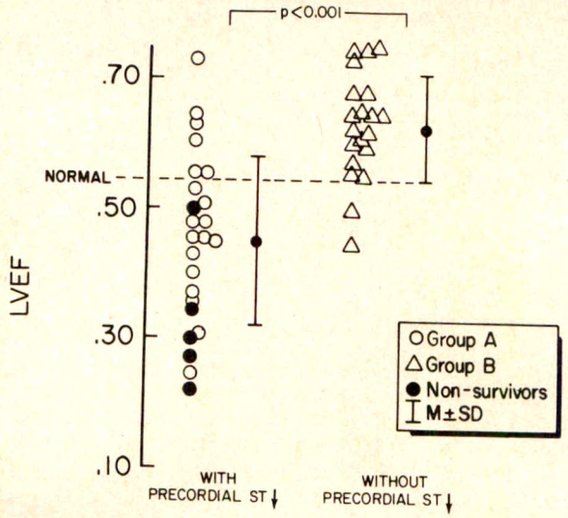


FIGURE 2. Representative 12 lead electrocardiogram and corresponding left ventricular ejection fraction (LV-EF) in a patient from Group A **(left)** and another patient from Group B **(right)**. The S-T segments are depressed in the precordial leads of the patient in Group A and are not depressed in the patient in Group B.



IGURE 3. Comparison of left ventricular ejection fraction (LVEF) in atients with (Group A) and without (Group B) precordial S-T depression ST↓]. The lower limit of normal ejection fraction is shown by the **roken horizontal line.** Ejection fraction is depressed in 18 of 24 pa- ents from Group A and in only 2 of 20 patients from Group B. M = ıean; p = probability; SD = standard deviation.

In eight patients in Group A precordial S-T segment epression, noted at the time of admission, had de- eased by 50 percent or disappeared entirely by the me radionuclide ventriculography was performed. The ıean value for the ejection fraction of these eight pa- ents was 0.50 ± 0.09, which was significantly higher (p 0.01) than that of the remaining 16 patients (0.42 ± 10) who had persistent S-T segment depression. Five atients in Group A but none in Group B manifested ectrocardiographic evidence of true posterior infarc- on, in particular, an R/S ratio in leads V_1 and V_2 of 1 greater. The mean ejection fraction of 0.42 in these ve patients was significantly different from the mean ılue in Group B (p <0.001) but not from the mean ılue of 0.46 in the remaining 19 patients in Group A ithout electrocardiographic signs of "true" posterior yocardial infarction.

Regional left ventricular wall motion: The mean data with respect to the differences in the abnormalities of regional wall motion between the two groups of patients are shown in Figure 4, left. The mean score of 42 ± 6 for Group A was significantly different (p <0.001) from that of 50 ± 4 for Group B. Eighteen (75 percent) of the 24 patients in Group A but only 5 (25 percent) of the 20 in Group B had abnormal wall motion of one or more infarct-related segments. Twelve patients in Group A and only 3 in Group B had severely abnormal (severe hypokinesia, akinesia or dyskinesia) wall motion of noninfarcted anteroseptal segments (p <0.05). Twenty patients in Group A but only 4 in Group B had abnormal apical wall motion (p <0.001). The average wall motion score was lower in Group A than in Group B not only in infarct-related segments (18 ± 4 versus 21 ± 3, p <0.02; Fig. 4), but also in anteroseptal (20 ± 3 versus 22 ± 2, p <0.05) as well as in apical segments (3 ± 1 versus 5 ± 1, p <0.001; Fig. 5).

Plasma peak MB creatine kinase changes: The mean level of 169 ± 94 IU/liter in Group A was about 50 percent higher than that of 83 ± 54 IU/liter in Group B (p <0.001) (Fig. 6).

Morbidity and mortality: Table III shows the incidence of in-hospital complications in the two subgroups of patients. Eleven patients from Group A but only one from Group B (p <0.01) either continued to experience ischemic chest pain or had recurrences 24 hours after admission to the coronary care unit. Clinically apparent congestive heart failure—indicated by post-tussive rales or third sound gallop, or both, developed in 12 (50 percent) subjects in Group A, but in no patient in Group B (difference statistically significant, p <0.01). Similarly, cardiogenic shock was present on admission in one patient from Group A and developed later in three others; it occurred in no patient in Group B. Furthermore, one patient from Group A had acute severe mitral regurgitation requiring valve replacement 2 weeks after admission.

Table III also contains the mortality figures for the entire group of 44 patients. The five in-hospital deaths were confined to patients from Group A, all occurring within 10 days of admission into the hospital. Severe

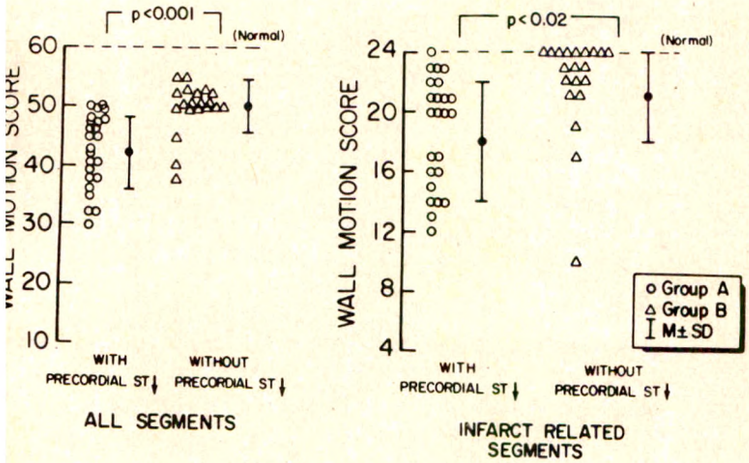


FIGURE 4. Regional wall motion. **Left,** total wall motion scores in Groups A and B. The score is relatively lower in Group A than in Group B. **Right,** wall motion score of infarct-related inferoposterior segments. One patient in Group A and eight in Group B had normal wall motion of infarct-related segments. The overall wall motion score of infarct-related segments is lower in Group A than in Group B. Abbreviations as in Figure 3.

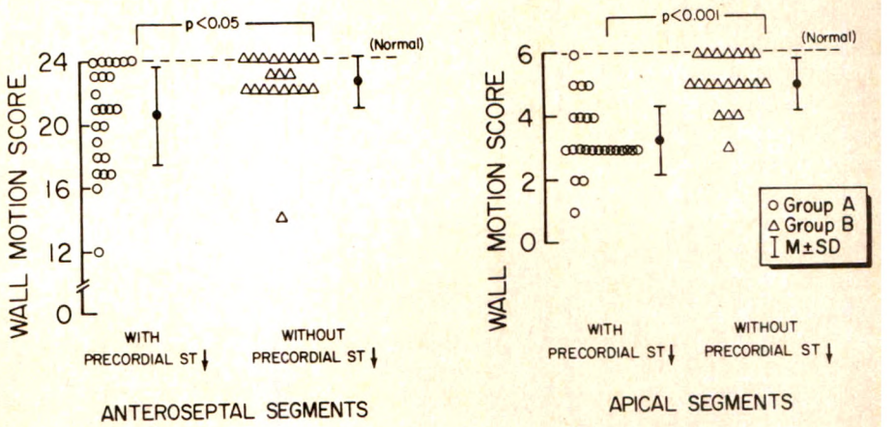


FIGURE 5. Regional wall motion of noninfarcted segments. **Left,** wall motion score of noninfarcted anteroseptal segments. The overall score is significantly lower in Group A than in Group B. Although wall motion score was abnormal in 12 of 20 patients from Group B and in 18 of 24 patients from Group A, severe wall motion abnormality was observed in 12 of 24 patients from Group A and in only 3 of 20 patients from Group B. **Right,** wall motion score in the apical segments. Note that 23 of 24 patients in Group A and only 13 of 20 patients in Group B had abnormal apical wall motion scores with overall scores being lower in Group A than in Group B.

congestive heart failure and shock were present in three of the five before death, with one patient dying of recalcitrant ventricular arrhythmias and the other of electromechanical dissociation.

Discussion

It is now reasonably well established that the severity of hemodynamic depression after acute myocardial infarction relates essentially to the extent of ischemic damage that occurs after coronary occlusion. Indeed, it has been shown that the size of infarct, estimated either enzymatically or established at autopsy, correlates closely with the overall prognosis of acute infarction.[7]

Subsets of inferior infarction: In the absence of ischemic damage sustained previously, acute inferior infarction as diagnosed by the standard electrocardiographic criteria generally has a more favorable prognosis than infarction involving the anterior wall because myocardial damage is less extensive.[1–3] However, some studies[8,9] have indicated that the prognosis in patients with inferior infarction is similar to or even worse than that of patients with anterior infarction. Such discrepancies in data suggest that the proportion of patients with high and low risk profiles differs in different population samples. Because the prognosis in coronary artery disease is determined largely by the degree of left ventricular dysfunction and severity of coronary disease,[10] it appears reasonable to predict that the prognosis would be poorer in patients with acute inferior infarction with greater left ventricular dysfunction than in those with relatively normal residual myocardial performance.

TABLE III

Major In-Hospital Complications in Groups A and B

Complications	Group A (n = 24)	Group B (n = 20)	p Value
Death	5*	0	<0.02
Congestive heart failure	12	0	<0.005
Postinfarction angina	11	1	<0.01

* Three patients died from cardiogenic shock, one patient from sudden electromechanical dissociation and one from primary refractory ventricular arrhythmias.

Our results with radionuclide ventriculography not only substantiate these predictions, but also provide a reasonably clear basis to account for the greater depression of left ventricular ejection fraction in the high risk subgroup than might be expected solely because of the inferior infarction. Of particular interest was the finding that the majority of high risk patients with inferior infarction can also be characterized by electrocardiographic criteria, namely, significant S-T segment depression in two or more anterior precordial leads accompanying the typical changes of acute inferior infarction.

Reciprocal S-T depression: The association, in most instances, of S-T segment depression in the anterior precordial leads with a significant reduction in ejection fraction and increased severity of segmental wall motion abnormalities indicates that such S-T de-

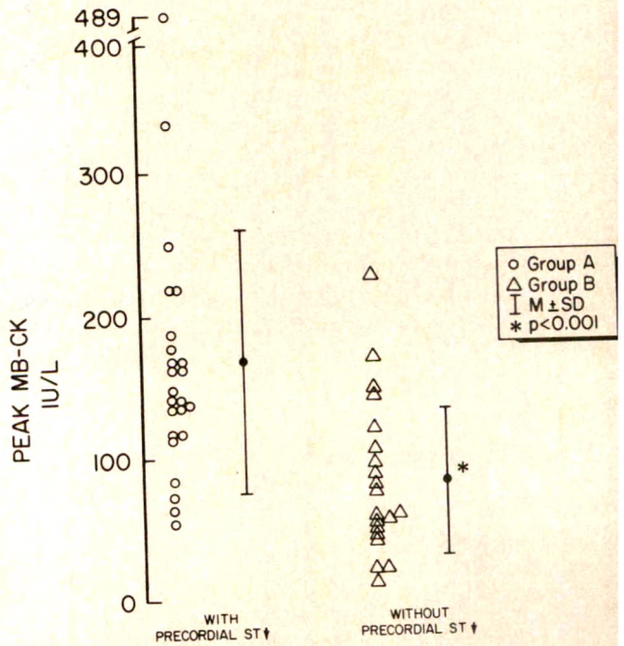


FIGURE 6. Peak plasma MB creatine kinase levels are significantly higher in Group A than in Group B.

pression can no longer be attributed to purely reciprocal electrical phenomena occurring in response to the inferior electrocardiographic changes. Our data suggest that they denote additional ischemia affecting either the true posterior wall or the remote anteroseptal portions of the left ventricle, or both. Such associated changes undoubtedly account for the significantly lower ejection fraction in the patients with those findings (Group A) than in the patients in Group B, who did not manifest these additional electrocardiographic and ventriculographic features.

Contractile function of remote myocardium: The depressed left ventricular ejection fraction in the high risk subset (Group A) may relate not only to the reduced contractile function of infarct-related segments but also to diminished performance of remote jeopardized ischemic segments of the left ventricle. Whether such additional anterior and anteroseptal wall motion abnormalities found in our Group A patients represent reversible ischemic dysfunction or nontransmural infarction is not clearly established from our data. However, the significantly higher peak plasma levels of MB creatine kinase in Group A than in Group B suggests that associated nontransmural infarction remote from the inferior wall or a larger inferoposterior infarction, or both, may play a role in contributing to more severe depression of left ventricular function in Group A patients. The reduction in the contractile performance of the left ventricular segments, remote from the main focus of inferior infarction, may also be due to the coexistence of reversible ischemic injury in the territories of blood supply of coronary arteries that may be severely stenosed but not occluded. This finding is in concordance with a previous report[11] in which approximately one third of patients who recovered from inferior myocardial infarction were found to have concomitant severe narrowing of the left anterior descending coronary artery.

The observed depression of regional contractile performance of putatively noninfarcted remote left ventricular segments is unlikely to be related to previous unrecognized infarction because none of our patients had historical or electrocardiographic evidence of prior myocardial infarction. Previous studies have demonstrated that performance of left ventricular segments remote from the infarcted segments may show variable degrees of hyper- or hypofunction.[12–15]

The problems associated with the delineation of the extent of infarction from the standard electrocardiogram should be emphasized. Anatomic studies have demonstrated electrocardiographic underestimation of the extent of healed necrosis.[16] However, our study demonstrates a high degree of correlation between S-T segment depression in precordial leads and the presence of regional dyssynergy in noninfarcted segments, raising the important possibility that the electrocardiographic criteria may be used reliably in detecting the high risk subset from the general group of patients with inferior myocardial infarction.

Limitations of the study: The 45° left anterior oblique and anterior projections used in this study allow clear assessment of wall motion of anteroseptal, apical and posterolateral left ventricular segments, but in some patients posterobasal segment 5 is not easily visualized in view of the overlapping right ventricle in the anterior view. We have recently found that this segment can be adequately visualized using a 70° left anterior oblique projection. It is therefore possible that in some of our patients the wall motion assessment of segment 5 may not have been accurate. However, it is unlikely that our results would have been materially affected by this limitation.

Clinical implications: The in-hospital clinical course of our patients with a depressed left ventricular ejection fraction was characterized by a high incidence rate of postinfarction ischemic chest pain, pump dysfunction and mortality. Patients who survived are being followed up for progress after their discharge from the hospital but, because their left ventricular ejection fraction was significantly depressed, their overall long-term prognosis is also likely to be compromised. Although our results indicate that a high risk subset of patients with inferior myocardial infarction can be characterized noninvasively, no data are available to suggest that aggressive therapy may alter morbidity and mortality in these patients. However, if the reversible nature of the regional dysfunction found in the remote and noninfarcted segments is confirmed by further studies, a rational basis will be established, for controlled clinical trials designed to salvage ischemic myocardium in the hope of favorably altering prognosis.

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Ergonovine Testing in a Coronary Care Unit

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This study describes the results of ergonovine testing in 100 consecutive patients who underwent this procedure in a coronary care unit. All patients had recently undergone coronary arteriography. A bolus injection of ergonovine was administered at 5 minute intervals in the following doses (mg): 0.0125, 0.025, 0.05, 0.1, 0.2, 0.3 and 0.4. The criterion for a positive test was the appearance of S-T elevation greater than 1 mm. The test was positive in all 17 patients known to have variant angina and in 18 (40 percent) of 45 patients who had a history of chest pain judged strongly suggestive of variant angina but who had no electrocardiogram recorded during pain. Of 38 patients with a history of chest pain classified as not entirely typical of variant angina, only 1 (2.6 percent) had a positive test.

Of the 64 patients with a negative ergonovine test, 47 had chest pain and 25 had nausea but none had more serious complications. Ventricular arrhythmia accompanied S-T elevation in 18 of the 36 patients with a positive test but occurred in only 4 of the 64 with a negative test ($p < 0.0005$). No patient needed treatment with antiarrhythmic drugs. Four of the 36 patients with a positive test had serious complications: severe transient hypotension (2 patients), recurrent episodes of angina with S-T elevation (1 patient) and a subendocardial infarction (1 patient). Thus, ergonovine testing is useful in patients with a typical clinical history of variant angina but without an electrocardiogram recorded during pain. In this study, a small but definite incidence of serious complications occurred during a positive test.

The administration of ergonovine maleate during coronary arteriography has been shown to be a sensitive and specific diagnostic test for variant angina.[1–6] In patients with documented variant angina ergonovine almost always induces angina with S-T segment elevation.[1–6] If coronary arteriography is repeated while angina and S-T elevations are present, severe coronary spasm is invariably found.[1–6] Because the actual visualization of coronary spasm is usually unnecessary, ergonovine testing could theoretically be performed at another time after coronary arteriography.

This study was undertaken to evaluate the feasibility and safety of ergonovine testing performed in the coronary care unit. In addition, this study defines (1) the sensitivity of the ergonovine test applied in this manner in patients with proved variant angina, and (2) the frequency of a positive test in patients with suspected but unproved variant angina.

Methods

Patients: The study group consisted of the first 100 consecutive patients who underwent ergonovine testing in our coronary care unit. There were 53 men and 47 women whose mean age was 49.5 years (range 24 to 71). Before the test all patients were classified on the basis of clinical history into one of three groups.

Group I: This group consisted of 17 patients with typical, well documented variant angina defined as unprovoked episodes of myocardial ischemic pain at rest, lasting less than 5 minutes, associated with transient S-T segment elevation,

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reversible with nitroglycerin and unassociated with evidence of myocardial necrosis. The clinical and angiographic characteristics of this group are listed in Table I. There were 13 men and 4 women; their mean age was 51.9 years (range 32 to 71). The electrocardiogram was normal in 10 of the 17 patients, revealed atrial fibrillation in 1 patient and isolated T wave abnormalities in 6. The electrocardiographic site of S-T segment elevation during spontaneous episodes of variant angina was anterior in nine patients, inferior in seven and both anterior and inferior in one patient. Coronary arteriography revealed entirely normal findings in five patients; isolated lesions of less than 50 percent of luminal diameter in three, one vessel disease (50 percent or greater stenosis) in three, two vessel disease in four, and three vessel disease in one; one patient had undergone surgery to bypass a single coronary stenosis. Left ventriculography disclosed normal findings in 14 patients and abnormal findings in 3 (Table I).

Groups II and III: The remaining 83 patients were referred by their cardiologist for ergonovine testing because of suspected variant angina. All 83 patients had a history of chest pain at rest compatible with myocardial ischemia but none had had a complete electrocardiogram recorded during pain. Before the ergonovine test a clinical history was obtained by the physician who performed the test and each patient was classified into either group II or group III. Group II consisted of patients whose clinical history was strongly suggestive of variant angina; patients with chest pain possibly due to variant angina but with at least one atypical clinical feature were assigned to group III. The distinction between groups II and III depended on the physician's interpretation of the patient's subjective account of symptoms; however, to increase uniformity, the classification decision was based on the following clinical features: the location, description and duration of chest pain episodes, the effect of nitroglycerin on chest pain (time to relief, reproducibility of effect) and the presence of other precipitating or relieving factors.

Group II contained 45 patients, 26 men and 19 women with a mean age of 50.3 years (range 24 to 66). The electrocardiogram was normal in 36 of the 45 patients, showed evidence of a previous transmural myocardial infarction in 2, T wave abnormalities in 5, left bundle branch block in 1 and atrial fibrillation in 1. Coronary arteriography revealed normal findings in 27 patients, one vessel disease (50 percent or greater stenosis) in 10, two vessel disease in 4 and three vessel disease in 2. The two remaining patients, one with one vessel disease and the other with three vessel disease, had undergone bypass grafting to each of the significantly diseased arteries. The left ventriculogram was normal in 39 of the 45 patients and abnormal in the other 6.

Of the 38 patients in group III, 14 were men and 24 were women. Their mean age was 47.5 years (range 35 to 65). The electrocardiogram was normal in 30 of the 38 patients, showed evidence of a previous transmural myocardial infarction in 2, abnormal T waves in 4, left bundle branch block in 1 and left anterior hemiblock in 1 patient. Coronary arteriography revealed normal findings in 29 patients, coronary stenoses of less than 50 percent in 1, one vessel disease in 2, two vessel disease in 4 and three vessel disease in 1. The remaining patient had undergone triple coronary arterial bypass grafting for three vessel coronary artery disease. The left ventricular angiogram was normal in 33 patients and abnormal in 5. Overall, group III contained more women, slightly younger patients and more patients with normal coronary arteriograms than did the other two groups.

Coronary arteriography: All patients had undergone coronary arteriography and left ventriculography before the ergonovine test. Selective coronary arteriography was performed with a percutaneous femoral approach using preformed catheters as previously described.[7] Particular care was taken to avoid catheter-induced coronary arterial spasm. No attempt was made during catheterization to induce coronary spasm by administering ergonovine. Nitroglycerin was not given before the initial dye injections; however, when a lesion was noted the vessel was filmed again in several views after administration of nitroglycerin. The left ventricular angiogram was filmed in the 30° right anterior oblique view before coronary arteriography. All angiographic films were routinely interpreted independently by an experienced cardiovascular radiologist. In counting the number of involved coronary arteries, a proximal stenosis of a large diagonal or marginal branch was considered as part of the left anterior descending or circumflex coronary arterial system, respectively.

Ergonovine testing: All ergonovine tests were performed in identical fashion according to the following protocol: An experienced physician and a nurse were continually present at the bedside throughout the test. A secure intravenous line was in place and an electrocardiographic monitoring oscilloscope was in view. Lead II was monitored except in patients with previously documented S-T segment elevation, in whom one of the leads that had demonstrated S-T elevation was monitored. Nitroglycerin (1.0 mg), lidocaine (100 mg), atropine (0.8 mg) and metaraminol (3.0 mg) were available at the bedside in prepared syringes for rapid intravenous administration. At 1 minute intervals cuff blood pressure and a 12 lead electrocardiogram were recorded, beginning 2 minutes before the first drug dose and continuing for a minimum of 5 minutes after the last injection. At 5 minute intervals a bolus injection of ergonovine was administered intravenously in this sequence: 0.0125, 0.025, 0.05, 0.1, 0.2, 0.3 and 0.4 mg. The criterion for a positive test was the appearance of an S-T segment elevation greater than 1 mm compared with the control tracing. An intravenous bolus injection of 0.3 mg of nitroglycerin was administered as soon as a positive response was detected or at the end of a negative test if diastolic blood pressure exceeded 100 mm Hg. Informed consent was obtained from each patient before the test.

Data analysis: The unpaired t test was used to compare the mean values of a single variable between two groups (for example, the dose of ergonovine administered to patients with anterior versus inferior S-T segment elevation). The paired t test was used to evaluate the significance of hemodynamic changes before and after ergonovine testing in patients with a negative test. In patients with a positive test a one way analysis of variance was applied to evaluate blood pressure and heart rate changes at four different points throughout the test. A chi-square analysis was used to determine whether the incidence of ventricular arrhythmia differed in positive compared with negative tests.

Results

Positive tests: The ergonovine test was positive in 36 of the 100 patients. The clinical, angiographic and ergonovine test data for these 36 patients are listed in Table I. Figure 1 illustrates the electrocardiographic changes during a highly positive test and Figure 2 shows the electrocardiogram during a minimally positive test.

The ergonovine test was positive in all 17 patients in group I (that is, those with previously documented variant angina). In 16 of the 17 patients, the electrocardiographic site of S-T segment elevation was the same as that during spontaneous episodes of variant angina: anterior in 8 patients, inferior in 7 and both

TABLE I

Data on Patients With a Positive Ergonovine Test

Case	Age (yr) & Sex	Coronary Arteriography (% stenosis)	Left Ventriculogram	Control ECG	Results of Ergonovine Tests: Site of Spontaneous ↑S-T	Site of ↑S-T During Test	Maximal Dose (mg)	Maximal ↑S-T (mm)
				Group I				
1	32M	LAD40	Normal	Normal	I, aVL, V_{1-6}	aVL, V_{2-5}	0.1	3.5
2	61F	LAD75,* RCA40	Normal	Normal	II, III, aVF	II, III, aVF	0.1	9
3	48M	LAD60	Normal	Normal	I, aVL, V_{1-4}	I, aVL, V_{1-5}	0.1	13
4	69M	Normal	Normal	Normal	II, III, aVF, V_{3-6}	II, III, aVF	0.025	6
5	47F	LAD90, RCA90	AK:anterolat, apical	T neg V_{1-3}	II, III, aVF	II, III, aVF	0.05	2
6	58M	Normal	Normal	Normal	II, III, aVF, V_{5-6}	II, III, aVF	0.1	2
7	50M	RCA40	Normal	Normal	V_{2-4}	II, III, aVF	0.4	2
8	42M	Normal	Normal	Normal	II, III, aVF, V_{5-6}	II, III, aVF	0.025	18
9	60M	LAD60	Normal	Normal	I, II, III, aVL, aVF, V_{1-6}	II, III, aVF, V_{2-5}	0.0125	24
10	44F	Normal	Normal	T neg II, III, aVF, V_{3-6}	V_{2-5}	V_{2-4}	0.1	2.5
11	62M	LAD90, RCA95, LCx90	Normal	T neg V_{1-6}	V_{1-4}	I, aVL, V_{1-6}	0.05	7
12	55M	LAD95, LCx99	Normal	T neg V_{2-4}	V_{1-4}	I, aVL, V_{1-6}	0.05	10
13	38M	Normal	Normal	Normal	II, III, aVF	II, III, aVF	0.3	1.5
14	54F	LAD80, LCx90	Normal	Normal	II, III, aVF	II, III, aVF	0.025	2.5
15	50M	LAD70	AK:anteroapical	T neg I, aVL, V_{3-6}	V_{2-4}	V_{2-5}	0.05	2
16	42M	LAD40	Normal	T neg I, II, aVL, V_{3-6}	V_{1-6}	V_{1-6}	0.025	2
17	71M	LAD90, D90, LCx50	AK:anterolat	Atrial fibrillation	I, aVL, V_{2-5}	I, aVL, V_{2-5}	0.1	1
				Group II				
18	35M	LAD70	HK:anterolat, apical	Normal	—	V_{1-3}	0.05	6
19	51M	LAD75*	Normal	T neg V_{1-4}	V_{1-3}	V_{1-3}	0.05	2.5
20	39M	LAD50, D70, RCA75	Normal	Normal	—	V_{1-4}	0.2	4
21	49M	LAD50, D75, LCx40	Normal	Normal	—	V_{1-3}	0.1	3
22	48M	LAD40, D50	Normal	↓S-T, T neg V_{2-5}	—	V_{1-4}	0.1	4
23	46F	Normal	Normal	Normal	V_2	I, aVL	0.1	1.5
24	66F	Normal	Normal	Normal	II, III, aVF	II, III, aVF	0.025	10
25	59M	Normal	Normal	T neg, II, III, aVF	II, III, aVF	II, III, aVF	0.025	8
26	39M	LCx90, RCA100	HK:inferior	Normal	—	V_1	0.2	2
27	47F	LAD60, LCx70	Normal	Normal	—	I, aVL, V_{2-6}	0.05	14
28	49M	LAD60, LCx65	Normal	Normal	V_{1-4}	aVL, V_{1-4}	0.05	7
29	58M	LAD50, LCx99, RCA80	Normal	Normal	—	II, III, aVF	0.2	3
30	59 F	RCA80	Normal	Normal	—	II, III, aVF	0.1	2
31	47M	Normal	Normal	Normal	—	I, aVL, V_{2-5}	0.2	5
32	59F	Normal	Normal	Normal	—	II, III, aVF	0.2	2
33	52M	LAD75,* C90,* RCA50*	Normal	Normal	—	II, III, aVF	0.2	2
34	61F	Normal	Normal	Normal	—	II, III, aVF	0.3	7
35	50M	LAD50, LCx40	HK:diffuse	LBBB	—	II, III, aVF	0.2	2
				Group III				
36	54F	LAD40, LCx40	Normal	Normal	—	II, III, aVF	0.4	1.5
				Mean ± Standard Deviation				
	51.4 ±9.4						0.12 ±0.1	5.4 ±5.2

* Artery with saphenous vein bypass graft.
AK = akinesia; anterolat = anterolateral; BP = blood pressure (mm Hg); C = circumflex coronary artery; D = diagonal branch; neg = negative; DK = dyskinesia; EGG = electrocardiogram; HK = hypokinesia; HR = heart rate (beats/min); LAD = left anterior descending artery; LBBB = left

nterior and inferior in 1. In one patient (Case 7), S-T egment elevation was recorded in leads V_2 to V_4 during pontaneous variant anginal episodes and in leads II, II and aVF during the ergonovine test.

In group II patients, whose clinical history was rongly suggestive of variant angina but without documentation, 18 (40 percent) of 45 had a positive test. In group III patients, whose clinical history included atypical features, only 1 (2.6 percent) of 38 patients had a positive test. Spontaneous S-T segment elevation during angina at rest was later documented in 5 patients of the 19 patients in group II or III who had a positive test. In the other 14 patients symptoms occurred infrequently and a complete electrocardiogram was never

TABLE I (continued)

Case	Control Before Test HR	Control Before Test BP	During Test, Before ↑S-T HR	During Test, Before ↑S-T BP	During ↑S-T HR	During ↑S-T BP	2 min post-NTG HR	2 min post-NTG BP	Arrhythmia During Test
				Results of Ergonovine Tests					
				Group I					
1	84	145/100	88	145/100	88	150/105	70	125/85	VE, bigeminy
2	84	125/80	84	120/80	84	110/70	64	60/40	VE
3	68	108/72	64	110/75	75	110/85	82	105/76	VE, pairs
4	62	170/110	64	170/110	74	190/120	84	175/110	None
5	60	100/65	65	116/66	68	105/70	102	110/66	None
6	72	110/80	73	120/90	58	115/85	61	110/80	None
7	58	150/100	64	160/105	60	120/90	67	130/90	SVE
8	85	175/115	87	180/110	90	170/120	86	170/110	None
9	66	120/70	63	115/70	58	120/90	72	125/70	VE, pairs
10	68	140/80	70	140/90	90	150/100	72	140/90	None
11	76	120/70	74	120/75	75	120/90	74	130/80	VE
12	86	140/90	90	160/100	110	164/100	78	160/100	VE
13	84	160/110	80	180/120	98	170/110	72	150/100	VE, pairs
14	77	156/100	71	170/100	73	170/98	86	160/100	None
15	53	130/90	49	140/80	49	130/90	57	120/90	None
16	59	150/90	57	150/90	68	160/110	62	130/90	VE, bigeminy
17	92	120/80	110	140/80	140	140/100	115	140/80	VE
				Group II					
18	47	135/78	61	110/70	54	130/90	52	122/75	VE, V tach
19	45	110/70	60	130/85	62	145/95	46	140/80	VE, bigeminy
20	75	134/90	80	160/104	78	170/110	95	160/105	None
21	64	120/80	60	125/80	64	160/100	68	150/100	None
22	70	100/65	76	140/90	86	150/90	80	120/85	None
23	65	118/70	75	124/84	81	130/85	82	120/84	VE, bigeminy
24	74	100/60	73	150/90	76	140/85	63	130/80	VE
25	43	130/90	45	120/80	48	130/80	55	110/80	VE, bigeminy
26	60	110/70	68	120/78	53	124/100	79	120/100	None
27	94	132/80	94	140/80	49	120/60	68	0/0	VE
28	71	130/80	70	110/70	79	130/90	74	140/90	VE, V tach
29	54	170/90	55	190/110	62	190/110	68	160/110	None
30	56	100/80	60	130/80	58	140/80	55	120/80	None
31	94	120/70	84	130/80	88	110/90	96	120/70	VE
32	78	132/86	68	140/92	67	135/95	74	132/90	VE
33	75	118/72	77	135/88	78	142/90	80	100/76	None
34	62	152/80	65	142/72	62	152/80	45	132/80	None
35	66	138/70	65	130/70	72	150/100	51	170/100	None
				Group III					
36	60	130/70	49	140/100	60	104/80	51	90/60	None
				Mean ± Standard Deviation					
	69.1 ±13.4	130.5/82.0 ±20.5 ± 13.6	70.5 ±13.6	138.9/87.2 ±21.2 ± 13.9	73.2 ±18.6	140.2/92.9 ±23.2 ± 13.4	71.8 ±15.8	127.1/83.4 ±32.3 ± 20.6	

bundle branch block; LCx = left circumflex coronary artery; NTG = 0.3 mg bolus injection of intravenous nitroglycerin; RCA = right coronary artery; SD = standard deviation; ↑S-T = S-T segment elevation; ↓S-T = S-T segment depression; SVE = supraventricular extrasystoles; T = T wave; VE = ventricular extrasystoles; V tach = ventricular tachycardia.

recorded during a severe episode of chest pain at rest. S-T segment elevation during chest pain was not noted in any of the 64 patients with a negative test.

Dose of ergonovine: Figure 3 illustrates the number of patients who had a positive test at each ergonovine dose level. In group I the test became positive (appearance of S-T segment elevation greater than 1 mm) in 15 of 17 patients at 0.1 mg or less of ergonovine. Overall, only 4 of the 36 positive tests occurred at the 0.3 or 0.4 mg dose level. The mean (± standard deviation) maximal dose of ergonovine for positive tests was 0.12 ± 0.1 mg. In patients in group I, the mean maximal ergonovine dose was 0.09 ± 0.1 mg, which was not significantly different from the mean maximal dose of 0.13

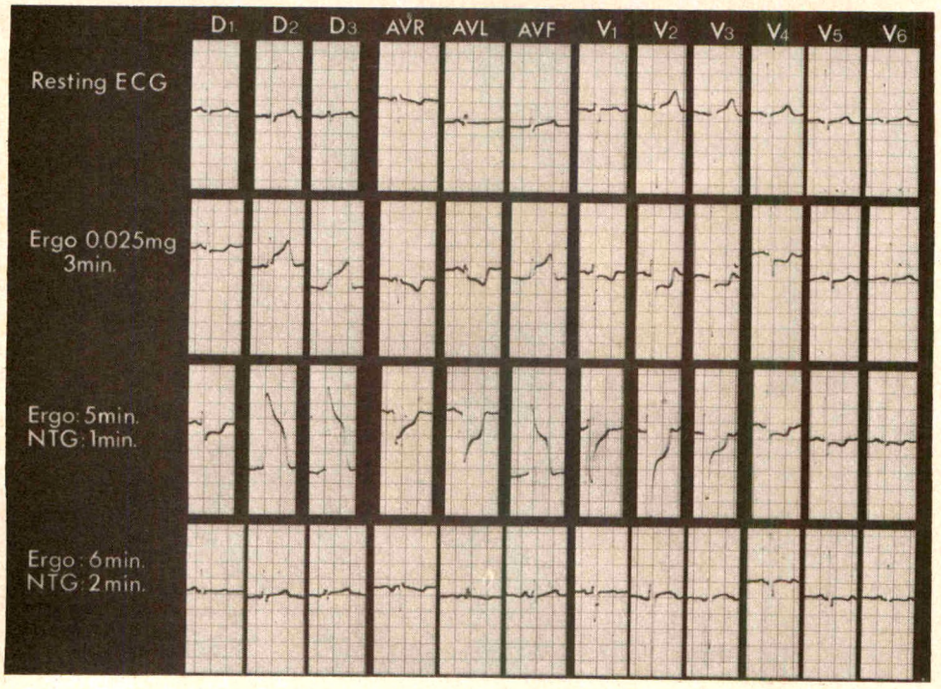


FIGURE 1. Patient 8. Electrocardiographic tracings from a highly positive ergonovine test. The control electrocardiogram (ECG) is normal. Three minutes after the 0.025 mg dose of ergonovine (Ergo), angina develops with S-T elevation in leads II, III and aVF (**second panel**). Two minutes later, 1 minute after an intravenous nitroglycerin (NTG) bolus injection, the degree of S-T elevation has increased (**third panel**). One minute later angina has disappeared and the S-T segment has returned to normal (**bottom panel**).

± 0.08 mg in patients in group II with a positive test. The maximal ergonovine dose for patients who manifested S-T segment elevation in the anterior electrocardiographic leads was 0.09 ± 0.06 mg, compared with 0.16 ± 0.13 mg for patients with S-T elevation in the inferior leads (difference not significant).

Complications: No serious complications occurred in the 64 patients with a negative test, although adverse effects were common. Forty-seven of these patients had chest pain during the test, usually atypical for angina and never associated with S-T segment changes. Twenty-five patients complained of nausea and in eight vomiting occurred. Five patients complained of headache. The diastolic cuff blood pressure increased to more than 100 mm Hg in 14 of the 64 patients at the end of the test. In each patient this abnormality caused no detectable adverse consequences; one or two intravenous bolus injections of 0.3 mg of nitroglycerin at the end of the test rapidly returned blood pressure to pretest levels in each instance. No important changes in heart rate or rhythm were detected during negative tests.

Serious complications occurred in 4 of the 36 patients with a positive test. In two patients (Cases 2 and 27) severe hypotension developed during S-T segment elevation after nitroglycerin administration. Both of these patients had abnormal coronary arteriograms; in one the site of S-T segment elevation was inferior and in the other it was anterior. Neither patient had heart block during ergonovine-induced S-T segment elevation but neither manifested reflex tachycardia as a response to the marked decrease in blood pressure. Both of these

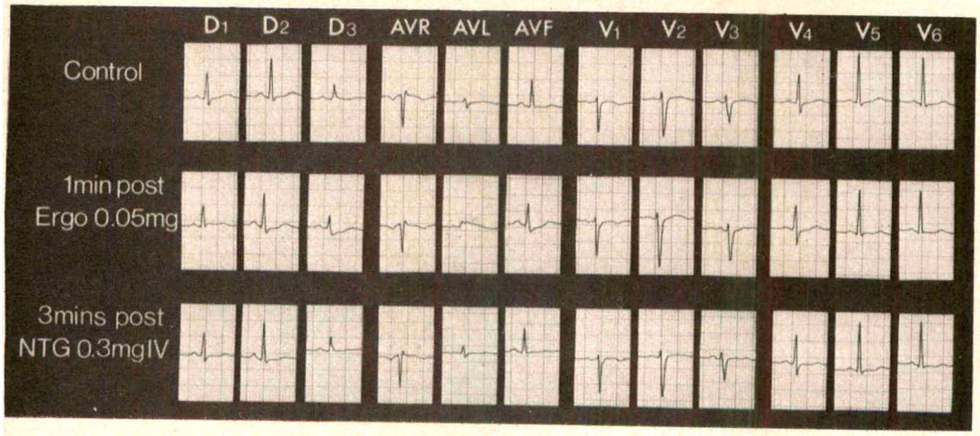


FIGURE 2. Patient 23. Electrocardiographic tracings from a minimally positive ergonovine test. The control electrocardiogram is normal. One minute after the 0.05 mg dose of ergonovine angina and ventricular bigeminy develop (**second panel**); the S-T segment is slightly elevated in lead I and elevated 1 mm in aVL. These changes disappeared after intravenous nitroglycerin (**bottom panel**).

patients received intravenous metaraminol; blood pressure and S-T segments returned to normal in less than 5 minutes and no adverse sequelae could subsequently be detected. In another patient (Case 29), angina with S-T segment elevation recurred several times during the 30 minutes after the test. Both the pain and S-T segment elevation promptly regressed each time after a bolus injection of 0.3 mg of nitroglycerin. The electrocardiogram was subsequently normal and no evidence of myocardial necrosis could be detected.

In Patient 12, a 95 percent proximal left anterior descending coronary arterial stenosis and a 99 percent circumflex arterial lesion were noted on arteriography. The control electrocardiogram showed negative T waves without Q waves in leads V_2 to V_4. Angina and S-T segment elevation in leads V_1 to V_4 developed during the ergonovine test but both disappeared in less than 4 minutes with a bolus injection of 0.3 mg of nitroglycerin. Angina did not recur, but for 2 hours after the test the blood pressure ranged from 170/110 to 190/120 mm Hg; thereafter, antihypertensive treatment was instituted. On the following day the electrocardiogram was unchanged but serum levels of creatine kinase and its isoenzyme and of lactate dehydrogenase were slightly elevated. A subendocardial infarction secondary to the prolonged hypertensive episode caused by the ergonovine test was diagnosed.

Ventricular arrhythmias were detected in 18 of the 36 patients with a positive test compared with 4 of 64 patients with a negative test ($p < 0.0005$). In eight of the patients with a positive test and in the four patients with a negative test, only isolated ventricular extrasystoles occurred. The most complex ventricular arrhythmia during a positive test was bigeminal rhythm in five patients, ventricular paired complexes in three patients and a short burst of ventricular tachycardia lasting less than 15 seconds in two patients. In each of the four patients with ventricular extrasystoles and a negative test the arrhythmia had been detected on other occasions and was thought to be chronic. In each of the patients with ventricular arrhythmia during a positive test, the arrhythmia developed coincident with angina and S-T segment elevation and in every instance it disappeared spontaneously when the S-T segment returned to normal. Antiarrhythmic drugs were not administered to any patient, although they were available at the bedside. No patient had second or third degree atrioventricular block or intraventricular conduction disturbances during the test.

Hemodynamic changes: In the 64 patients with a negative test, the cuff blood pressure increased from 129.9 ± 21.6/81.6 ± 11.2 mm Hg 1 minute before the test to 156.6 ± 26.7/94.6 ± 15.5 mm Hg ($p < 0.0005$) 4 minutes after the last dose of ergonovine. Heart rate in this group did not change significantly, from 68.9 ± 12.8 beats/min before to 70.4 ± 12.6 after the test.

In the 36 patients with a positive test, the cuff blood pressure was 130.5 ± 20.5/82.0 ± 13.6 mm Hg before the test (the same as in patients with a negative test). After the administration of ergonovine but before the occurrence of angina or S-T segment elevation, blood pressure had increased to 138.9 ± 21.2/87.2 ± 13.9 mm Hg. During S-T segment elevation a further slight increase in blood pressure, particularly diastolic pressure, to 140.2 ± 23.2/92.9 ± 13.4 mm Hg was noted. At 2 minutes after the administration of an intravenous bolus injection of 0.3 mg of nitroglycerin the blood pressure had decreased to 127.1 ± 32.3/83.4 ± 20.6 mm Hg. The changes in blood pressure throughout the test were highly significant ($p < 0.0005$). A small, clinically unimportant increase in heart rate occurred in this group during the test (from 69.1 ± 13.4 before to 70.5 ± 13.6 after ergonovine administration, but before S-T segment elevation to 73.2 ± 18.6 during S-T segment elevation). Two minutes after nitroglycerin administration the heart rate had decreased slightly to 71.8 ± 15.8/min.

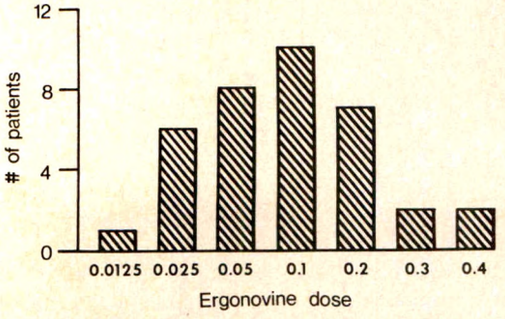


FIGURE 3. Number of patients with a positive test at each ergonovine dose level. Thirty two of the 36 tests were positive at a dose of 0.2 mg or less.

Correlation with angina: The criterion for a positive test in this study was the appearance of S-T segment elevation. This finding occurred in 36 patients, 34 of whom had coexistent angina. Two patients (Cases 8 and 14) had S-T segment elevation without angina during the test; both had had documented episodes of transient S-T segment elevation at rest, with and without angina. The onset of angina was coincident with the onset of S-T segment elevation in 19 patients; angina slightly preceded S-T elevation in 11 patients and S-T elevation preceded the onset of angina in 4 patients.

No patient in this study had angina with coexistent S-T segment depression during the ergonovine test, unless S-T segment elevation also occurred. In most patients who had marked S-T elevation reciprocal S-T segment depression was noted in other leads (Fig. 1). In only one patient (Case 31) was S-T segment depression detected before the onset of S-T elevation; this patient had angina together with 2 to 3 mm S-T depression in leads V_3 to V_6 1 minute before the onset of S-T elevation in leads I, aVL and V_2 to V_5. This sequence of changes was reproducible on a subsequent ergonovine test in this patient.

Discussion

Although the administration of ergonovine in the coronary care unit has previously been described,[8,9]

ergonovine tests are usually performed during coronary arteriography.[1–6] This study describes the results of ergonovine testing in the coronary care unit in 100 consecutive patients with suspected or documented variant angina who had previously undergone coronary arteriography. In each case incremental doses of ergonovine were administered at 5 minute intervals beginning with a dose of 0.0125 mg and increasing to 0.4 mg if a positive response was not detected. The criterion for a positive test was the appearance of S-T segment elevation of greater than 1 mm compared with that in the control electrocardiogram.

Sensitivity and Specificity

Sensitivity: The ergonovine test was positive in all 17 patients with previously documented variant angina, demonstrating that the sensitivity of the test is excellent when it is performed as in this study. This sensitivity is probably dependent on the amount of ergonovine administered, the criteria for a positive response and the level of symptom activity in the patients studied. Theoretically, ergonovine-induced coronary spasm could occur without S-T segment elevation, producing a negative test according to the criterion of our study but a positive test using angiographic criteria. In the study of Heupler et al.,[3] 2 of the 10 patients with variant angina and ergonovine-induced coronary spasm had no coincident S-T segment abnormalities. Because all 17 patients with variant angina in our study had a positive test using the criterion of S-T segment elevation, sensitivity in our study does not appear to be limited by this problem, possibly because of the larger cumulative dose of ergonovine that we administered. However, some of the patients that we tested may have had undetected coronary spasm at lower dose levels, before the electrocardiographic manifestations of ischemia appeared. Theoretically, the sensitivity of the ergonovine test when performed during coronary arteriography could be decreased by the vasodilatory effect of the angiographic contrast medium. Finally, the frequency of variant anginal episodes appears to correlated with the results of ergonovine testing[9]; thus, sensitivity likely depends on the symptom level in the patients with variant angina under study. In our experience when patients with a previously positive test are retested after a long asymptomatic interval, many have a negative result.[10]

Specificity: In this study, as in previous studies, the exact specificity of the ergonovine test is difficult to define, because an unexpectedly positive response may not be a false positive result but a reflection of atypical or undocumented variant angina. Thus, 3 of 66 patients with "angina-like chest pain" in the study of Heupler et al.[3] had a positive test and in each case the authors concluded that coronary spasm was probably the cause of chest pain. None of the 19 patients without variant angina studied by Curry et al.[4] had a positive test; one of 35 patients with atypical chest pain in the study of Schroeder et al.[1] had coronary spasm. We obtained similar results: Only 1 of the 38 patients in our group III (those with a clinical history not entirely typical of variant angina) had a positive test.

The frequency of a positive test was 40 percent (18 of 45) in patients in group II, in whom variant angina was strongly suspected but not documented. Some of these tests may be false positive cases, but in five patients variant angina was later documented and in none of the others has a complete electrocardiogram been recorded during a spontaneous episode of severe chest pain at rest. These considerations suggest that the specificity of ergonovine testing as performed in this study is probably satisfactory; however, the design of the study does not provide a definitive answer to this question.

Indications

A diagnostic ergonovine test is indicated in patients whose clinical history is highly suggestive of variant angina although S-T segment elevation has not been documented (our group II). In this study, 40 percent of such patients had a positive test. Confirming the diagnosis of variant angina is clinically important in these patients, because the institution of specific treatment with calcium antagonist drugs can eliminate episodes of variant angina even in most patients who do not respond to long-acting nitrates.[9,11–15] In patients with less typical symptoms (group III) ergonovine testing produces a low yield of positive tests (less than 3 percent in this study) and thus is not routinely indicated. However, in some of these patients with disabling chest pain ergonovine testing can be useful to eliminate the unlikely possibility of variant angina. In patients with documented variant angina (group I), an ergonovine test is not necessary for diagnostic purposes.

Complications

In most patients the administration of ergonovine causes a dose-related increase in systolic and diastolic arterial pressure. A reflex decrease in heart rate usually does not occur, probably because of a countervailing chronotropic effect of the drug. Nausea, vomiting and chest pain frequently occur during negative tests and appear to be dose-related. In this study, no other complications occurred in the 64 patients with a negative test.

Arrhythmias: Because ergonovine-induced episodes of variant angina are similar to spontaneous episodes,[16] ventricular arrhythmias and A-V block could be expected to complicate positive tests. Indeed, half of our patients with a positive test had ventricular arrhythmias during S-T segment elevation, including two patients who had short bursts of ventricular tachycardia; however, in every instance the arrhythmia spontaneously disappeared when the S-T segment returned to normal. No patient required treatment with antiarrhythmic drugs. Second or third degree A-V block did not occur in any patient.

Myocardial ischemia and infarction: In addition to these expected events, more serious complications were noted in four patients. The combination of transmural myocardial ischemia and intravenous nitroglycerin administered as a bolus injection caused transient but severe hypotension in two cases. The absence of an appropriate reflex increase in heart rate in these two patients is similar to the atypical response

reported by Come and Pitt[17] in five patients with acute myocardial infarction treated with nitroglycerin. After the administration of an intravenous vasopressor, arterial pressure and S-T segments returned to normal within 5 minutes. In another patient, recurrent episodes of angina with S-T segment elevation, relieved by nitroglycerin, occurred over a 30 minute period after the ergonovine test. In none of these three patients did the complications cause permanent sequelae. However, in the fourth patient with a complication a subendocardial infarction developed after the ergonovine test. A severe proximal fixed coronary stenosis was present in this patient and severe hypertension persisted for 2 hours after the test; this combination probably caused the subendocardial infarction, because angina and S-T elevation during the ergonovine test lasted for less than 4 minutes. This complication might have been prevented if antihypertensive therapy had been instituted more promptly.

Role of fixed coronary stenosis: Among the 36 patients with a positive test, 21 had fixed coronary lesions greater than 50 percent and each of the 4 patients with complications was in this group. Complications did not occur in any of the 15 patients without significant fixed stenoses. Since the end of this study we have performed 113 additional positive tests using this protocol; the only patient with a complication in this second series had severe fixed lesions. These observations suggest that complications during ergonovine testing may be limited to patients with fixed coronary lesions. Because the test appears to be more dangerous in association with multiple severe fixed obstructions, we no longer use it in patients with these findings.

Previously reported incidence of complications: Serious complications were not reported in the initial studies[1–6] of ergonovine testing performed during coronary arteriography and the number of patients with a positive test in these studies totals more than 50. Two of the groups[2,3] responsible for these studies originally recommended that the test be performed only during coronary arteriography because of the potential for serious complications; however, one of these two groups now perform some tests outside the catheterization laboratory if the coronary anatomy is known.[14,18] Recently, Buxton et al.[19] reported several deaths caused by intractable coronary spasm after ergonovine administration during coronary arteriography and suggested that intracoronary nitroglycerin should be available for this circumstance. Both in our present study and in our subsequent experience[10,20] using our ergonovine test protocol (a total of 149 positive tests), no patient has had angina and S-T elevation that did not regress within 5 minutes after an intravenous bolus injection of nitroglycerin. We believe that the 5 minute interval between doses and the comparatively small initial doses of ergonovine used in our protocol accounts for its relative safety.

Limitations of the Study

The patients tested in this study are not representative of most patients with coronary artery disease; therefore, our results may not be applicable to patients with typical exertional angina or severe multivessel disease. The normal response to ergonovine, an increase in afterload, a generalized decrease in coronary arterial diameter without focal spasm and an increase in coronary resistance, would be expected to induce angina with S-T depression in some patients with severe coronary disease, as found by Stein and Weinstein[21] in 1950. None of the patients in our study had S-T depression in the absence of S-T elevation.

Although all of our patients with documented variant angina had S-T elevation in response to ergonovine, an additional method of detecting myocardial ischemia during the test would be useful, particularly in patients with severe coronary lesions. Cross-sectional echocardiography[22] or radioisotopic left ventriculography performed in conjunction with the ergonovine test could thus provide clarification or confirmation of the test results. Finally, in patients with severe coronary disease or left ventricular dysfunction, ergonovine testing might cause more frequent complications than found in this study.

Present Recommendations

On the basis of these data we recommend (1) that ergonovine testing be performed either in a coronary care unit environment in patients with known coronary anatomy or during coronary arteriography, (2) that patients with multiple severe fixed obstructions not be tested, (3) that the initial ergonovine dose be limited to 0.0125 or 0.025 mg, (4) that ergonovine not be administered more often than at 5 minute intervals, and (5) that angina with S-T elevation be treated immediately with intravenous or intracoronary nitroglycerin. If the first ergonovine dose used is 0.05 mg or more, the test should probably be performed in the catheterization laboratory because intracoronary nitroglycerin may be required. Further experience is required to determine which components of the test procedure cause complications.

Acknowledgment

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Clinical Relevance of Exercise-Induced S-T Segment Elevation

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Patients with exercise-induced S-T elevation or S-T depression were evaluated with demographic, treadmill and angiographic data. When 541 patients with S-T depression were compared with 109 patients with S-T elevation, a greater proportion of the former had chest pain (71 versus 58 percent) and a normal-sized ventricle (86 versus 61 percent) with normal wall motion (54 versus 30 percent). A greater proportion of patients with S-T elevation had had a previous myocardial infarction (61 versus 33 percent). Among patients without prior infarction (360 with S-T depression and 42 with S-T elevation), these differences disappeared. In this group of 42 patients with S-T elevation, 83 percent had a normal-sized ventricle, 64 percent had normal contractility and none had a ventricular aneurysm; the severity of coronary disease and ventricular dysfunction did not differ from the severity in patients with S-T depression. Thus, in patients without prior myocardial infarction, the cause of the development of S-T elevation or S-T depression during exercise does not appear to be related to the severity of the coronary lesions, ventricular function or wall abnormalities at rest. In patients with prior myocardial infarction, exercise-induced S-T elevation appears to be a marker of depressed left ventricular function.

Although exercise-induced S-T segment elevation has been reported for more than 10 years,[1,2] the number of studies and patients investigated has been small. The clinical significance and the cause of S-T segment elevation remain unsettled. Several abnormalities associated with this elevation have been described, including left ventricular aneurysm,[3,5] variant angina,[6,7] severe ischemic disease[2,8] and left ventricular wall abnormalities.[4] Exercise-induced S-T segment elevation is rarely seen in asymptomatic healthy persons.[9]

About two thirds of the patients reported on had had a previous myocardial infarction, and were thus more likely to have had left ventricular aneurysm, wall motion abnormalities or severe coronary artery disease. A recent study[10] suggested that among patients without prior myocardial infarction, there are no distinguishing demographic differences between patients with S-T segment elevation and those with depression. Wall motion at rest was reported as normal in most patients with S-T elevation.

This study expands and quantitates information concerning patients with exercise-induced S-T elevation with or without prior myocardial infarction and further compares these subgroups with corresponding subgroups of patients with exercise-induced S-T depression.

Methods

Study patients: At the time of this analysis, the Duke Computerized Information System contained prospectively collected data regarding treadmill testing, coronary angiography and contrast left ventriculography in 2,590 patients.[11,12] Our study group consisted of those 650 patients whose only criteria for entry into the study were a positive exercise tolerance test and diagnostic cardiac catheterization performed between November 1, 1972 and January 1,

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TABLE I

Comparison of Patients With S-T Depression and S-T Elevation

	S-T↓	p Value	S-T↑
Patients			
Number	541		109
Age (yr) (mean ± SD)	50.6 ± 9.2	= 0.21	49.8 ± 8.2
M/F ratio	6:1	= 0.14	9:1
Chest pain (%)*	71	<0.02	58
Reason treadmill test terminated (%)			
Angina	27	<0.03	17
Fatigue	35	= 0.66	33
ECG changes	25	= 0.19	25
Dyspnea	10	= 0.09	16
Peak HR (beats/min) (mean ± SD)	135 ± 26		138 ± 26
Exercise stage achieved	2.4 ± 1.1		2.3 ± 1.1
Normal-sized ventricle (%)	86	<0.0001	61
Normal contractility (%)	54	<0.0003	30
Wall motion abnormality (%)	45	<0.0001	64
Aneurysm (%)	1	<0.0002	6
LMC obstr. (%)	8	= 0.77	9
Vessels with CAD (mean ± SD)	2.0 ± 1.0	= 0.24	2.3 ± 0.9
Ejection fraction			
<0.40 (%)	11	<0.0001	31
>0.40 (%)	89	<0.0001	69
Previous MI (%)	33	<0.0001	61

* Chest pain indicates development of angina-like pain on exercise whether or not it resulted in termination of treadmill test.

CAD = coronary artery disease; ECG = electrocardiographic; HR = heart rate; LMC obstr. = obstruction of left main coronary artery; M/F = male/female; MI = myocardial infarction; p = probability; SD = standard deviation; S-T↓ and S-T↑ = S-T segment depression and elevation, respectively.

1979. Patients who had congenital heart disease, idiopathic hypertrophic subaortic stenosis or valvular heart disease other than mild mitral regurgitation were excluded. The patients are a selected group in that Duke is a major referral center. However, the reasons for referral are probably no different from those made to many cardiologists and include problem chest pain of unknown cause, assessment and treatment recommendations for patients with angina, or assessment o young patients with myocardial infarction. All patients wh had undergone treadmill testing or cardiac catheterizatio were entered into the computerized system.

Treadmill exercise procedure: The exercise tolerance tests were obtained using the graded multistage Bruce protocol,[13] with patients in the fasting state. Patients were monitored continuously with four standard electrocardiographic leads, and at each stage full 12 lead electrocardiograms were recorded. Leads in which S-T segment elevation or depression occurred were noted, as were peak heart rate, exercise stage achieved, reason for terminating the test, and the presence or absence of chest pain. The treadmill test was considered positive if there was horizontal or downward sloping S-T segment depression of 0.1 mV or greater than 80 ms after the J point; in the presence of S-T depression in the control tracing, additional depression greater than or equal to 0.2 mV was required. These changes had to occur in the absence of drug or electrolyte abnormalities known to induce them. A test was also considered positive if there was 0.1 mV or more elevation in the S-T segment in response to exercise. This criterion was applied whether the S-T segment at rest was isoelectric or already elevated. All patients with any S-T elevation had their records examined individually. Patients in whom both S-T elevation and depression occurred were included in the group with S-T elevation. There were 541 patients with S-T depression and 109 patients with S-T elevation. Blood pressure was measured using standard arm cuff sphygmomanometers in each stage and every 2 minutes after exercise until it stabilized.

Catheterization data: Cardiac catheterization included right and left heart catheterization, biplane left ventriculography and selective coronary arteriography. The Judkins technique was used unless a contraindication existed, in which case the Sones technique was used. Ventricular volumes were calculated using biplane analysis as previously described.[14] Before 1974, specific volume data were not collected and ventricular size was scored as normal or mildly, moderately or massively enlarged. Ejection fraction was not routinely calculated for all patients before 1974, although data for this variable during and after 1974 were available. Significant coronary disease including the left main coronary artery was defined as a luminal narrowing of 75 percent or more. Lesions were defined by the consensus of three experienced angiographers.

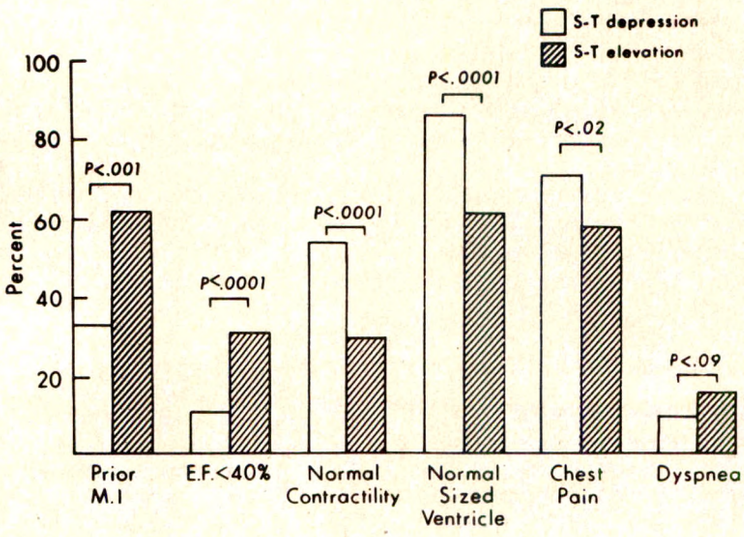


FIGURE 1. All patients with S-T depression or S-T elevation induced by exercise. Chest pain refers to the development of chest pain during treadmill testing whether or not it was the reason for terminating the test. Dyspnea refers to the reason for terminating the test. E.F. = ejection fraction; M.I = myocardial infarction; P = probability.

TABLE II

Demographic and Treadmill Test Data

	Prior MI			No Prior MI		
	S-T↓	S-T↑	p	S-T↓	S-T↑	p
Patients						
Number	181	67		360	42	
Age (yr) (mean ± SD)	51.2 ± 8.6	47.9 ± 8.1	<0.008	50.3 ± 9.4	52.8 ± 7.5	= 0.07
M/F ratio	12:1	16:1	= 0.62	4:1	6:1	= 0.60
Chest pain (%)	68	46	<0.004	66	69	= 0.67
Reason test terminated (%)						
Angina	32	19	<0.05	24	12	= 0.08
Fatigue	31	37	= 0.34	37	26	= 0.15
Dyspnea	11	18	= 0.15	10	12	= 0.62
ECG changes	28	15	<0.03	23	40	= 0.02
Peak HR (beats/min) (mean ± SD)	130 ± 24	141 ± 22		138 ± 26	132 ± 26	
Exercise stage achieved (mean ± SD)	2.3 ± 1.0	2.5 ± 1.1		2.1 ± 1.1	1.8 ± 0.9	

Abbreviations as in Table I.

Wall motion abnormalities were defined using biplane angiography and were scored qualitatively as asyneresis when systolic wall motion was less than normal, akinesia when no systolic movement occurred and dyskinesia when paradoxical systolic motion occurred. An aneurysm was defined as a paradoxical systolic bulge with a neck, seen on angiography. Wall motion was defined as normal, abnormal or aneurysm formation.

Prior myocardial infarction was defined as a convincing clinical history along with significant (40 ms) Q waves in the electrocardiogram at rest.

Statistical analyses were performed using chi-square contingency tables or the unpaired *t* test as appropriate.

Results

Demographic, treadmill and angiographic data for the groups with S-T depression and S-T elevation (Table I): There were no significant differences in age, male/female ratio, peak heart rate achieved or exercise stage attained in the two groups. Significant differences were evident in the treadmill data. Patients with S-T depression were more likely to have exercise terminated because of angina and were more likely to have chest pain during the treadmill test. Significant differences also were found in the cardiac catheterization data for the two groups. Those with S-T depression were more likely to have a normal-sized ventricle with normal wall motion and to have a normal to mildly reduced ejection fraction (Fig. 1).

The group with S-T elevation had significantly more patients with previous myocardial infarction. Because this might account for the other differences observed between the two groups, we analyzed the same variables after separating each group into two subsets—those with and those without myocardial infarction. There were 181 patients with and 360 without prior myocardial infarction in the group with S-T depression, and 67 with and 42 without prior infarction in the group with S-T elevation. The demographic and treadmill data are shown in Table II, the angiographic data in Table III.

When patients with prior infarction were excluded, there were no longer significant differences between patients with S-T depression and those with S-T elevation in the proportion who manifested chest pain or terminated the treadmill test because of angina, fatigue or dyspnea, although in a greater proportion of patients with S-T depression the test was stopped because of

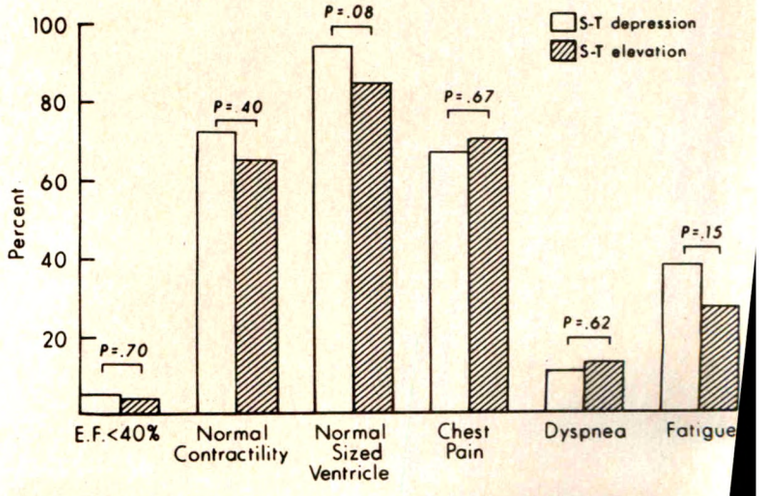


FIGURE 2. Patients with no previous myocardial infarction. Dyspnea and fatigue refer to reasons for terminating the treadmill test. Chest pain refers to the development of chest pain whether or not it was the reason for terminating the test.

electrocardiographic changes. Similarly, there were no angiographic differences between patients with S-T elevation or depression when the patients with prior myocardial infarction were excluded (Fig. 2).

In the subgroup with S-T elevation and no previous myocardial infarction three patients (all women) were found to have normal coronary arteries and one patient had reversible coronary spasm documented. However, there was no systematic attempt to induce coronary spasm in this group. In the subgroups with prior myocardial infarction there were differences between patients with S-T elevation and those with S-T depression. In patients with S-T elevation the exercise test was less likely to be stopped because of angina or electrocardiographic changes, and angiographic data in this group revealed that there were fewer patients with a normal-sized ventricle, fewer with normal contractility, more with an ejection fraction of less than 40 percent and more with ventricular aneurysm (Fig. 3).

Concomitant S-T depression and S-T elevation: The routine use of 12 lead electrocardiograms permitted us to determine the frequency of concomitant S-T depression in the group with S-T elevation. Concomitant S-T depression was noted in 55 percent in the subgroup with no previous myocardial infarction, but in 37 percent of those with previous infarction. The location of the S-T segment elevation in the 12 lead electrocardiogram also permitted us to seek an association between the location of the S-T elevation and the location of the coronary lesions (Table IV). The most striking finding was that S-T elevation in leads V_1 to V_3 was always associated with a significant lesion in the left anterior descending artery. S-T elevation in leads V_4 to V_6 was associated with a left anterior descending lesion in 16 of 17 of those with a prior myocardial infarction.

S-T elevation in electrocardiogram at rest: In the group with previous myocardial infarction and exercise-induced S-T elevation there were persistent S-T elevations (at rest) from the time of the infarct in the control tracings in 43 patients (64 percent), 5 (12 percent) of whom had an aneurysm. There were no persistent S-T elevations at rest in 24 patients (36 percent), 1 (4 percent) of whom had an aneurysm. Overall, 9 percent (6 of 67) patients had an aneurysm, compared with 2 percent of patients with S-T depression and previous myocardial infarction. In the group with no previous myocardial infarctions but with exercise-induced S-T elevation only one patient had minor S-T elevation at rest.

Finally, when the group with previous myocardial infarction and exercise-induced S-T elevation was separated into those with isoelectric S-T segment and S-T elevation at rest, there were no differences in reasons for terminating the treadmill test. Fatigue was found in 59 versus 49 percent ($p = 0.52$), dyspnea in 21 versus 19 percent ($p = 0.09$) and the development of chest pain in 20 versus 17 percent ($p = 0.59$), respectively. There was no difference in exercise stage achieved or peak heart rate during the treadmill test. In comparing the angiographic data in these same groups the only statistically significant difference occurred in the percent of patients with normal ventricular contractility; normal ventricular function was noted in 20 percent of those with an isoelectric S-T segment at rest versus 2 percent of those with S-T elevation at rest ($p = 0.01$).

Discussion

The association of exercise-induced S-T segment elevation with ventricular wall motion abnormalities at rest[4] and aneurysm has been well described.[3–5] However, the studies reported contained many patients with previous myocardial infarction, raising the possibility that this association may be a result of the patient group studied. Our results and those of Longhurst and Kraus[10] demonstrate that the findings of the previous studies were indeed influenced by the large proportion of patients with prior myocardial infarction. This study, for the first time, quantitates and compares clinical, treadmill and angiographic data of patients with exer-

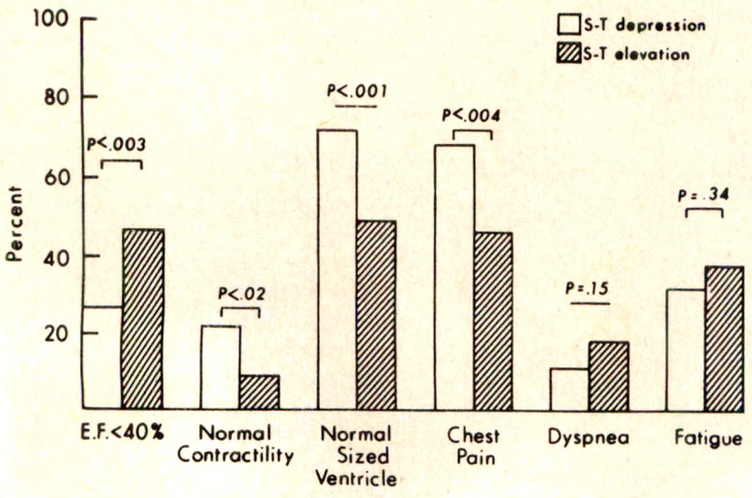


FIGURE 3. Patients with a previous myocardial infarction. Dyspnea and fatigue refer to reasons for terminating the treadmill test. Chest pain refers to the development of chest pain whether or not it was the reason for terminating the test.

TABLE III

Angiographic Comparisons

	Prior MI			No Prior MI		
	S-T↓	S-T↑	p	S-T↓	S-T↑	p
Normal-sized ventricle (%)	72	49	<0.0001	93	83	= 0.08
Normal contractility (%)	22	9	<0.02	71	64	= 0.40
Wall motion abnormality (%)	76	82	<0.02	29	36	= 0.65
Aneurysm (%)	2	9	<0.007	0	0	
LMC obstr. (%)	8	4	= 0.31	9	16	= 0.09
Ejection fraction						
<0.40 (%)	27	47	<0.003	4	3	= 0.70
≥0.40 (%)	73	53	<0.003	96	97	= 0.70
Vessels with CAD (mean ± SD)	2.3 ± 1.0	2.3 ± 0.8	= 0.52	1.8 ± 1.2	2.2 ± 1.0	= 0.11

Abbreviations as in Table I.

cise-induced S-T elevation versus those with S-T depression in groups with and without prior myocardial infarction.

S-T elevation versus S-T depression induced by exercise: In the subgroups with no previous myocardial infarction, we found no differences in demographic, treadmill or angiographic data. In the group with S-T elevation, wall motion at rest was normal in two thirds, there were no ventricular aneurysms and coronary disease was not more severe than in the group with S-T depression. Thus, no distinguishing features could be found that might explain why some patients have S-T elevation as opposed to S-T depression in response to exercise. The possibility that new wall motion abnormalities with exercise account for the S-T segment elevation cannot be ruled out by our study; however, radionuclide angiographic studies[15–17] have demonstrated that left ventricular wall motion abnormalities during exercise are a common response to ischemia when the S-T segments are depressed and not elevated. Thus, the factors determining the directional changes of the S-T segments with exercise in these patients remain poorly understood. As noted in the study by Longhurst and Kraus[10] the development of S-T segment elevation was associated with significant coronary artery disease in 87 percent of patients without prior infarction, which is similar to the 93 percent incidence rate found in this study.

Patients with a previous myocardial infarction tend to have a larger ventricle and poorer contractility, and their exercise is more often limited by fatigue or shortness of breath. Comparisons within this subgroup reveal that those with S-T elevation are more likely to have more severe left ventricular dysfunction than those with S-T depression (that is, fewer with normal contractility, fewer with ejection fraction above 40 percent, and more with aneurysm formation).

Role of coronary spasm: The role of coronary spasm in the production of exercise-induced S-T elevation cannot be defined from this study. A recent report[18] found ergonovine-induced spasm in 10 of 11 patients with suspected or documented variant angina and exercise-induced S-T elevation. The applicability of these findings to a larger group of patients without suspected variant angina but with exercise-induced S-T elevation is unknown. Although we did not routinely attempt to provoke spasm in our group, only one case of spasm was documented.

Role of ischemia in opposite wall (reciprocal S-T elevation): A possible explanation for S-T segment elevation in the group with prior myocardial infarction is that ischemia in an opposite wall, which would be detected as S-T depression with epicardial electrodes on that wall, manifests itself as a reciprocal change (that is, S-T elevation when assessed by a surface electrode overlying an electrically neutral area of myocardial fi-

TABLE IV

Association Between Site of S-T Segment Elevation and Location of Coronary Arterial Lesions

	Prior MI						No Prior MI					
Site of S-T↑	Cases	RCA	LAD	LCx	LMC	2–3 VD	Cases	RCA	LAD	LCx	LMC	2–3 VD
V_{1-3}	22	14	22	15	2	18	21	12	21	8	2	13
V_{4-6}	17	8	16	10	0	10	5	1	2	2	0	2
I, aVL	5	4	5	4	0	4	4	3	4	2	1	4
aVR	1	1	1	1	0	1	5	5	3	3	3	5
II, III, aVF	10	10	9	7	1	9	1	1	1	1	0	1
Multiple	12	9	9	6	0	9	6	4	3	2	1	3

LAD = left anterior descending artery; LCx = left circumflex artery; LMC = left main coronary artery; MI = myocardial infarction; RCA = right coronary artery; 2–3 VD = 2 or 3 vessel disease.

brosis). However, this appears to be an untenable hypothesis because only 37 percent of patients had concomitant S-T depression in the 12 lead electrocardiogram. The finding of both S-T depression and S-T elevation in the same patient emphasizes that unless a full 12 lead electrocardiogram is obtained there may be misclassification of patients with S-T depression in isolated monitoring leads who have elevation in other leads. The site of S-T elevation accurately predicts the location of certain specific coronary lesions, especially in leads V_1 to V_3; all patients with this finding had significant left anterior descending arterial lesions whether or not they had a prior myocardial infarction.

Implications: The previously reported association between wall motion abnormalities and exercise-induced S-T elevation appears to be a function of the patient group studied. In patients without a previous myocardial infarction, subgroups with S-T depression and S-T elevation do not differ with respect to ven tricular wall motion abnormalities at rest or the severit of coronary disease. The reason for the development c S-T elevation in a small group remains unclear an should be investigated. In the group with a previou myocardial infarction, the electrophysiologic feature producing S-T elevation compared with S-T depressio are also unknown, but S-T elevation appears to defin a group with a large prevalence of ventricular dysfunc tion.

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Nonfatal Myocardial Infarction in Medically Treated Patients With Coronary Artery Disease

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The purpose of this study was to identify patient characteristics associated with nonfatal myocardial infarction as the first event after cardiac catheterization in medically treated patients with coronary artery disease. Multiple logistic risk analysis of 81 baseline characteristics in 354 patients who died or had nonfatal infarction identified 10 characteristics (5 clinical and 5 cardiac catheterization variables) as independently discriminating between the two events. Left ventricular function, specific coronary anatomy, previous myocardial infarction and age were the most important discriminators. Poor left ventricular function and left main coronary stenosis were associated with death. Subtotal left anterior descending and right coronary arterial stenosis, normal hemodynamics, absence of previous infarction and young age were associated with nonfatal infarction. Thus, in any subset of patients who have a uniform risk of ischemic events (nonfatal infarction or death), nonfatal infarction is most likely to occur in those who are young, have had no previous infarction, have subtotal left anterior descending and right coronary arterial stenosis and normal hemodynamics.

Several studies[1–10] have documented the incidence of nonfatal and fatal myocardial infarction in patients with coronary artery disease. However, little is known about the factors that are specifically associated with nonfatal infarction. Because myocardial infarction may have a fatal or nonfatal outcome, the incidence of nonfatal infarction in a population will depend on both the incidence of ischemic events and the survival rate from those events. To determine which patients have nonfatal infarction it is appropriate first to determine which patients experience ischemic events and then to identify the factors that distinguish nonfatal infarcts from fatal events.

In a recent study,[11] we identified coronary anatomy, progressive chest pain and left ventricular function as the most important predictors of ischemic events (nonfatal infarction and death) in 1,214 medically treated patients. The ratio of nonfatal to fatal events varied considerably across subsets defined by those predictors. Having identified the predictors of ischemic events, we undertook this study to identify formally the factors associated with nonfatal infarction as opposed to death. Eighty-one baseline characteristics were analyzed in 354 patients who experienced an ischemic event to identify variables that discriminated between fatal and nonfatal events. The resulting discriminators were then applied to patients with three vessel coronary artery disease, who have a large incidence of ischemic events, to identify subsets of patients with a large incidence of nonfatal infarction.

Methods

Patient group and baseline data: The patient group consisted of 1,214 symptomatic medically treated patients with significant coronary artery disease. The group was recently analyzed to identify independent predictors of survival[12] and total incidence of ischemic events (death or nonfatal infarction).[11] The 1,214 patients represented those treated medically among the 1,993 consecutive pa-

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TABLE I
Outcome Events in 1,214 Symptomatic Medically Treated Patients with Coronary Disease

Initial Cardiovascular Event	n	Other or Subsequent Events	n
Nonfatal infarction	135	Cardiovascular death subsequent to nonfatal infarction	36
Cardiovascular death	219	Noncardiovascular death	14
Total	354		50

tients who underwent cardiac catheterization at Duke University Medical Center between November 1969 and January 1978 because of recurrent chest pain and were found to have significant coronary artery disease. Significant coronary artery disease was defined as 75 percent or greater obstruction of the luminal diameter of one or more major coronary arteries.[13] All data were collected prospectively and stored in a computerized information system.[14] The baseline characteristics analyzed in this study were the same 57 noninvasive clinical characteristics and 24 cardiac catheterization descriptors analyzed in the recent reports.[11,12]

Follow-up: All patients were followed up 6 and 12 months after cardiac catheterization, and annually thereafter, by a staff cardiologist during a clinic visit or by a research associate by telephone. All patients had been followed up for at least 12 months, and overall the follow-up data of the 1,214 patients were 99 percent complete. The method of collecting and verifying information about deaths and nonfatal infarction has been described in detail elsewhere.[11] Briefly, patients were asked about new hospitalizations and possible ischemic events at each follow-up period. A patient's physician was contacted for further information when a patient died or there was any possibility that an ischemic event had occurred. Fatal and nonfatal myocardial infarctions were documented by electrocardiographic and serum enzyme criteria.[11] A myocardial infarction was considered nonfatal if the patient was discharged from hospital.

TABLE II
Independent Discriminators Between Nonfatal Infarction and Death as Initial Events

	Adjusted Chi-Square Value*
Left ventricular end-diastolic pressure	5.98
Left main stenosis	5.88
History of myocardial infarction	9.07
Total right coronary occlusion	9.00
Arteriovenous oxygen difference	9.33
Total left anterior descending occlusion	5.31
Pulse bruit	5.72
Right bundle branch block	5.57
Age	5.53
Stable chest pain	4.41

*Chi-square >3.84, $p < 0.05$; Chi-square >6.63, $p < 0.01$.
The total chi-square value for all 10 variables (−2 log likelihood ratio) was 107.07, with $p = 0.0278$ when judged with 81 degrees of freedom. This indicates that obtaining 10 significant variables in 81 candidates was not a spurious finding.

Outcome events during the follow-up period are listed in Table I. Two nonfatal infarcts and two initial cardiovascular deaths occurred after the analysis of total events.[11] Patients who had an initial nonfatal infarction and subsequently died were counted as having an initial nonfatal event. There were 354 initial cardiovascular events consisting of 135 (38 percent) nonfatal infarcts and 219 (62 percent) deaths.

Data analysis: To identify characteristics that distinguished nonfatal from fatal events, we analyzed 81 baseline characteristics of the 354 patients who experienced an event with a multiple logistic risk model.[15,16] This multivariable analysis was performed by the same stepwise strategy that we have previously applied to survival analysis with the Cox regression model.[12] Briefly, variables that provided the best discrimination between nonfatal and fatal events were successively included in a statistical model until no remaining variable contributed independent information that was significant at a 5 percent level.

To establish the clinical importance of characteristics that were significant independent discriminators between the two events, we examined the proportions of nonfatal and fatal events related to the individual descriptors and to selected combinations of these descriptors. The ability of these discriminators to define subsets of patients with a large incidence of nonfatal infarction was examined in patients with three vessel coronary disease, a group that has a large incidence of ischemic events.

Cumulative survival rates and event rates were calculated with use of life table methods[17] in the manner previously described.[11] The event-free rate and its complement, the initial event rate, were calculated using death and nonfatal infarction as terminating events. The initial event rate has two components, initial death rate and nonfatal infarct rate.[11]

Results

Independent Discriminators Between Nonfatal and Fatal Events

Characteristics identified by multivariable analysis as significantly and independently discriminating between nonfatal and fatal events are listed in order of selection in Table II. The interpretation of this order is that the best single variable for discriminating between a fatal and nonfatal event is the first one selected. The next variable selected is the one that in combination with the first forms the best pair of variables. For example, the best four variable combination for distinguishing between the two events would be left ventricular end-diastolic pressure, left main coronary stenosis, history of myocardial infarction and total right coronary arterial occlusion. The chi-square statistics reported in Table II are based on the final combination and provide a measure of the influence of each characteristic after adjusting for all other variables selected.

Clinical (noninvasive) characteristics: Five of the significant variables were clinical characteristics. History of previous myocardial infarction was the third variable selected in the model whereas the other four clinical characteristics were the last variables selected in the model. Of the 194 patients with a history of myocardial infarction who had an ischemic event, 28 percent had a nonfatal infarct; whereas 51 percent of the 160 patients with no history of myocardial infarction had a nonfatal infarct. The relation between age and

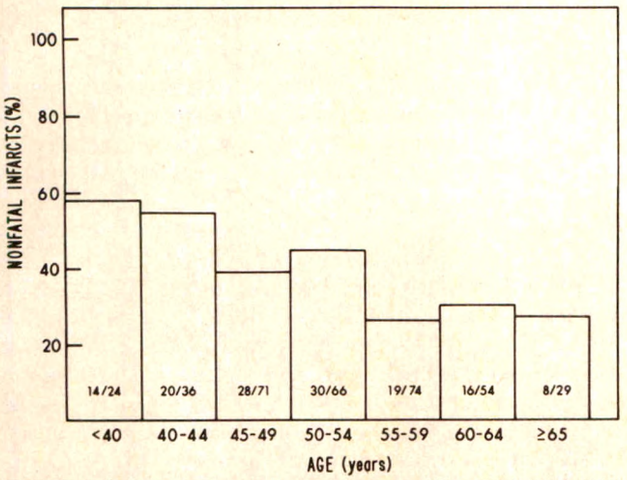


FIGURE 1. Relation between age and the proportion of total ischemic events that were nonfatal infarcts. The **figures within each bar** indicate the ratio between the number of nonfatal infarcts and the total number of events (nonfatal infarcts and deaths).

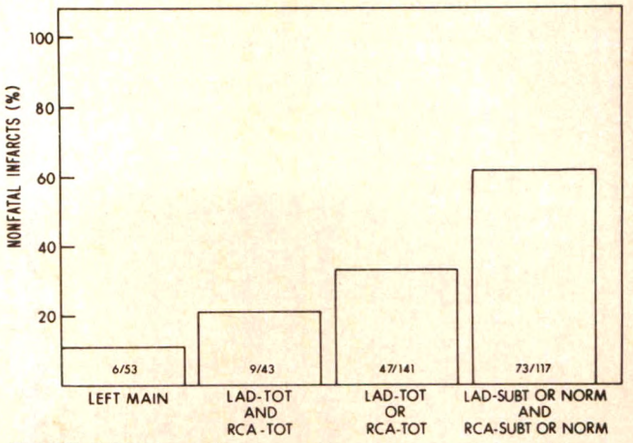


FIGURE 2. Relation between specific coronary anatomy and the proportion of ischemic events that were nonfatal infarcts. The anatomic categories are mutually exclusive. Ratios as in Figure 1. LAD = left anterior descending artery; NORM = normal; RCA = right coronary artery; SUBT = subtotal stenosis; TOT = total occlusion.

outcome is illustrated in Figure 1. In patients less than 45 years old, 57 percent of the events that occurred were nonfatal, whereas in patients 55 years and older, only 27 percent were nonfatal. Pulse bruits and right bundle branch block were associated with the smallest (25 percent) and largest (67 percent) proportion of nonfatal events but were present in only 59 and 12, respectively, of the 354 patients. Stable chest pain was the least significant variable and only slightly improved the discrimination.

Invasive characteristics: *Coronary anatomy:* The relation between outcome and the independently significant descriptors of coronary anatomy is illustrated in Figure 2. In patients with significant left main coronary stenosis, only 6 (11 percent) of 53 events were nonfatal. Patients with left main coronary stenosis were excluded from the other anatomic categories. In patients with total occlusion of both the left anterior descending and right coronary arteries, 9 (21 percent) of 43 events were nonfatal; in those with total occlusion of either of these arteries but not both, 47 (33 percent) of 141 events were nonfatal; and in those with total occlusion of neither artery (that is, with a subtotally occluded or normal left anterior descending and subtotally occluded or normal right coronary artery), 73 (62 percent) of 117 events were nonfatal.

Hemodynamic function: The relations between outcome and left ventricular end-diastolic pressure and arteriovenous oxygen difference are illustrated in Figures 3 and 4, respectively. Nonfatal infarcts were as frequent as death in patients with normal hemodynamic findings and accounted for 46 percent of ischemic events

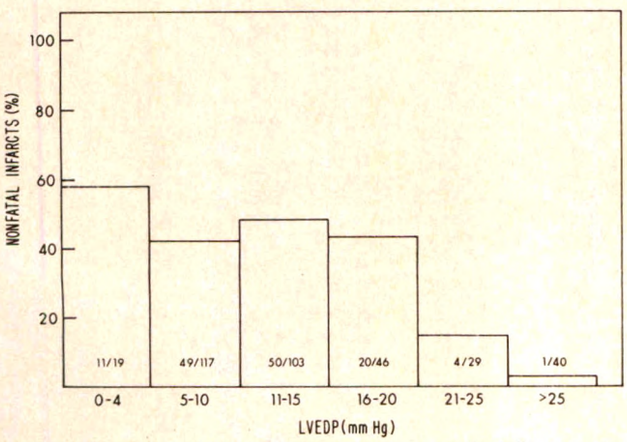


FIGURE 3. Relation between left ventricular end-diastolic pressure (LVEDP) and the proportion of ischemic events that were nonfatal infarcts. Ratios as in Figure 1.

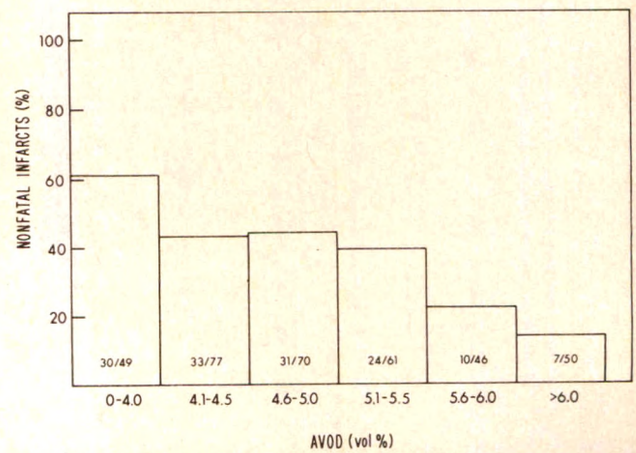


FIGURE 4. Relation between arteriovenous oxygen difference (AVOD) and the proportion of ischemic events that were nonfatal infarcts. Ratios as in Figure 1.

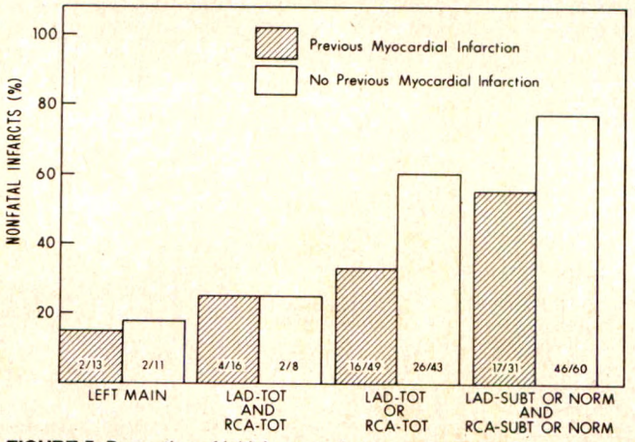


FIGURE 5. Proportion of initial events that were nonfatal infarcts related to history of previous myocardial infarction and specific coronary anatomy in patients with left ventricular end-diastolic pressure of 20 mm Hg or less and arteriovenous oxygen difference of 5.5 volumes or less. Ratios as in Figure 1. Abbreviations as in Figure 2.

in patients with a left ventricular end-diastolic pressure of less than 20 mm Hg and in patients with an arteriovenous oxygen difference of less than 5.5 volumes percent. The proportion of nonfatal infarcts decreased to 7 percent in patients with an end-diastolic pressure of more than 20 mm Hg and to 18 percent in patients with an arteriovenous oxygen difference of more than 5.5 volumes percent.

Combined clinical and catheterization characteristics: The effect of the combination of history of previous infarction and specific coronary anatomy in distinguishing between outcomes in patients with normal hemodynamic findings (left ventricular end-diastolic pressure 20 mm Hg or less and arteriovenous oxygen difference 5.5 volumes percent or less) is illustrated in Figure 5. In patients with neither total occlusion of the left anterior descending or right coronary artery nor a history of previous infarction, 46 (77 percent) of 60 ischemic events were nonfatal.

Independent Discriminators as Predictors of Nonfatal Infarction

There were 521 patients with three vessel coronary disease in the total group of 1,214 patients. The effect of subgrouping these patients using the characteristics that distinguished nonfatal infarction from death is illustrated in Figures 6 and 7.

Patients with normal left ventricular function: The 3 year rate of ischemic events in 137 patients with three vessel disease and normal left ventricular function was 22 percent. When these patients were subgrouped into patients with subtotal stenosis of the left anterior descending and right coronary arteries and patients with total stenosis of either or both of these arteries, the 3 year rates for total ischemic events were similar: 21 and 24 percent, respectively (Fig. 6). However, in the patients with subtotal stenosis, 71 percent of the initial events were nonfatal infarcts and the 3 year nonfatal infarct rate was 15 percent; in contrast, among patients with total stenosis, only 42 percent of the initial events were nonfatal infarcts and the 3 year nonfatal infarct rate was 10 percent.

When the patients with three vessel disease, normal left ventricular function and subtotal stenosis of the left anterior descending and right coronary arteries were further subgrouped into those who had no previous infarction and were also aged less than 55 years, there were 32 patients with a 3 year total ischemic event rate of 25 percent. Eighty-four percent of the events were nonfatal infarcts and the 3 year nonfatal infarct rate was 21 percent.

Patients with impaired left ventricular function: The 3 year ischemic event rate in 383 patients with three vessel disease and moderately impaired left ventricular function was 34 percent. When these patients were classified into those with subtotal stenosis of the left anterior descending and right coronary arteries and those with total stenosis of these vessels, the 3 year ischemic event rates were 36 and 33 percent, respectively (Fig. 7). Again, despite similar event rates, the nonfatal infarct rates varied with specific coronary

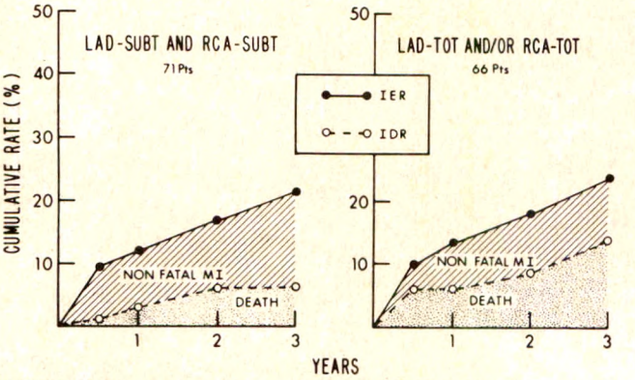


FIGURE 6. Specific coronary anatomy and the incidence of ischemic events in patients with three vessel coronary artery disease and normal left ventricular function. At each interval, the rate of nonfatal myocardial infarct (MI) is represented by the difference between the initial event rate (IER) and the initial death rate (IDR). Pts = patients; other abbreviations as in Figure 2.

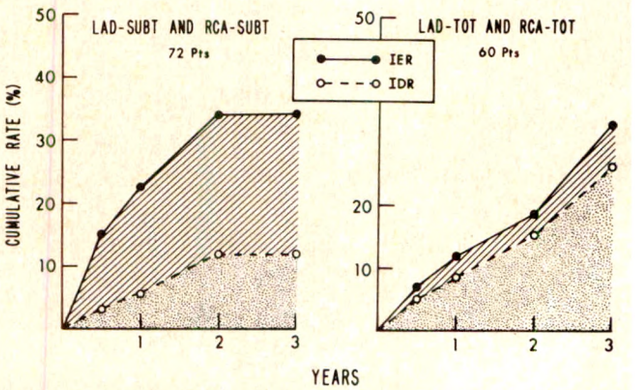


FIGURE 7. Specific coronary anatomy and the incidence of initial ischemic events in patients with three vessel coronary artery disease and moderately impaired left ventricular function. Abbreviations as in Figure 6.

anatomy. Thus, in patients with subtotal stenosis, 70 percent of initial events were nonfatal infarcts and the 3 year nonfatal infarct rate was 24 percent; whereas in patients with total stenosis, 18 percent of the initial events were nonfatal infarcts and the 3 year nonfatal infarct rate was only 6 percent.

Patients with three vessel disease, moderate left ventricular dysfunction and subtotal left anterior descending and right coronary arterial stenosis could not be subgrouped according to age and previous infarction. However, in 30 patients with no history of previous infarction, the 2 year rate of nonfatal infarcts was 35 percent without taking age into account.

Discussion

This study confirms that ischemic events in patients with left main coronary arterial stenosis or severely impaired left ventricular function are predominantly fatal. In the absence of these characteristics, age, history of previous myocardial infarction and the specific anatomy of the left anterior descending and right coronary arteries appear to be the most important factors for distinguishing nonfatal from fatal events.

Age: Other studies[3,18] have identified age as an important predictor of outcome in coronary artery disease. We have not found age to be an independent predictor of either survival[12] or ischemic events[11] when other important characteristics such as the cardiac catheterization findings are taken into account. This study indicates that although age may not influence the overall incidence of ischemic events, within a subset that has a uniform rate of ischemic events, younger patients tend to have a nonfatal infarction whereas older patients tend to die.

Previous myocardial infarction: An association between previous myocardial infarction and subsequent fatal events is also well established.[19,20] This association may be due to an increased propensity to arrhythmic death after myocardial infarction.[21,22]

Coronary anatomy, previous myocardial infarction and left ventricular function: In the 1,214 medically treated patients, coronary anatomy, previous myocardial infarction and left ventricular function were closely associated. Of those with abnormal left ventricular function, 78 percent had historical or electrocardiographic evidence, or both, of previous infarction, whereas of those with total occlusion of the left anterior descending and right coronary arteries, 87 percent had abnormal left ventricular function. In contrast, only 49 percent of patients with subtotal stenosis of these arteries had abnormal ventricular function. Despite these associations, the fact that the descriptors of coronary anatomy and previous infarction were significant in the multivariable analysis indicates that they contributed independent discriminatory information over and above their association with left ventricular function. Thus, coronary anatomy and history of previous infarction distinguished between nonfatal and fatal events in subgroups of patients homogeneous with respect to left ventricular function.

Left ventricular ejection fraction, an important prognostic factor in coronary artery disease,[18,23,24] was not analyzed in this study because it was not measured in all patients. Several variables reflecting left ventricular function emerged as significant discriminators between nonfatal infarction and death. It is likely that left ventricular ejection fraction is also important for distinguishing between the two outcomes.

Exercise test results predict both survival[25] and total ischemic events.[26] Whether exercise testing can distinguish between nonfatal and fatal events was not addressed in our study because not all patients underwent such testing. The answer will depend on future studies.

Nonfatal versus fatal ischemic events: The results of the multiple logistic risk analysis indicate that within any group of patients with a uniform risk of ischemic events, the patients who are young, have not experienced a previous infarct and have subtotal left anterior descending and right coronary arterial stenosis are most likely to have a nonfatal infarction. In contrast, older patients with previous infarction who have total left anterior descending and right coronary arterial stenosis and poor left ventricular function are most likely to die.

If the variables that predict ischemic events[11] are combined with the variables that distinguish between nonfatal and fatal events, patients with a high risk of nonfatal infarction can be identified. The incidence of total ischemic events increases with worsening coronary anatomy and left ventricular function. Patients with left main coronary stenosis or severely impaired left ventricular function have predominantly fatal events. Therefore, patients with three vessel disease who have normal or only moderately impaired left ventricular function are most likely to have a nonfatal infarction. When our patients were further categorized according to the characteristics that distinguished nonfatal infarction from fatal events, the overall incidence of ischemic events did not change, but the proportion of events represented by nonfatal infarction and the rate of nonfatal infarction increased.

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Platelet Function Studies in Coronary Heart Disease. IX. Increased Platelet Prostaglandin Generation and Abnormal Platelet Sensitivity to Prostacyclin and Endoperoxide Analog in Angina Pectoris

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Platelet prostaglandin generation (malondialdehyde production) and platelet sensitivity to prostacyclin (a vasodilator and platelet aggregation inhibitor) and to epoxymethanodienoic acid (EMA) (a vasoconstrictor and platelet aggregation stimulant endoperoxide analog) were studied in patients with angina pectoris and in control subjects. Platelet malondialdehyde production was higher in patients than in control subjects (mean ± standard error of the mean 2.50 ± 0.30 versus 1.70 ± 0.13 nmol/10^9 platelets, $p < 0.02$). Platelets from patients were significantly less sensitive to prostacyclin's antiaggregatory effects than were those from control subjects (amount of prostacyclin required for 50 percent platelet aggregation inhibition 1.90 ± 0.35 versus 0.68 ± 0.05 ng, $p < 0.02$). Furthermore, less EMA was required to induce 50 percent platelet aggregation in patients with angina pectoris than in the normal subjects (133 ± 8 versus 194 ± 16 ng, $p < 0.001$). These observations suggest that increased platelet prostaglandin generation and abnormal platelet sensitivity to prostacyclin and endoperoxide analog in certain patients with coronary artery disease are important potential mechanisms in the pathogenesis of myocardial ischemia.

The syndrome of angina pectoris results from an imbalance between myocardial oxygen demand and supply. Mechanisms such as coronary arterial spasm[1–3] and excessive adrenergic activity have been implicated in the initiation of myocardial ischemia. Recently, several investigators[4,5] have suggested that abnormalities of platelet function may be related to genesis or extension, or both, of myocardial ischemia and infarction. Increased in vivo platelet aggregate formation may occlude the coronary arteries[5,6] and impede blood flow, resulting in decreased oxygen supply, while oxygen demand is unaltered. In states of health, products of arachidonic acid metabolism, thromboxane A_2 (a vasoconstrictor) and prostacyclin (a vasodilator), derived through the prostaglandin endoperoxide, balance each other's vascular effects.[7–11] In addition, the platelet proaggregatory effects of thromboxane A_2, generated by platelets, are counteracted by the antiaggregatory effects of prostacyclin produced by the vessel wall.

An excessive production of platelet prostaglandins may be expected to produce tissue ischemia by causing vasocontriction and in vivo platelet aggregate formation. Likewise, a decrease in platelet sensitivity to prostacyclin or an increase in sensitivity to thromboxane A_2, or both, may be pathogenic in myocardial ischemia in patients with coronary artery disease. We studied patients with a history of angina pectoris and normal subjects with respect to platelet prostaglandin synthesis and platelet sensitivity to prostacyclin and an endoperoxide analog in order to examine possible mechanisms in the pathogenesis of myocardial ischemia.

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Methods

Study subjects: Twenty-two patients aged 44 to 71 years (mean 55) with a history of angina pectoris were studied. All had historical and electrocardiographic evidence of myocardial ischemia. All had been hospitalized for chest pain and were at bed rest in the coronary care unit and had abstained from smoking for at least 6 hours (six were habitual smokers). Ten of these patients (group A) were studied during a spontaneous episode of angina pectoris; the remaining 12 patients (group B) had their last episode of chest pain 2 to 24 hours before collection of blood for platelet studies. Frequency and severity of chest pain were similar in both groups. Significant coronary arterial luminal narrowing (more than 50 percent) was present in the 18 patients who later underwent coronary angiography. Two patients had coronary spasm in atherosclerotic vessels (Table I). No patient had diabetes mellitus.

Fourteen normal subjects (aged 34 to 70 years) without a history of clinical coronary artery disease served as the control group. No patient or normal subject had taken aspirin or any other platelet-active drug for 10 days before the study. No normal subject had smoked in the preceding 6 hours (four were habitual smokers).

Platelet Studies

Blood was collected from the patients and control subjects at rest in the postabsorptive state. In seven patients, studies were repeated 24 to 72 hours later when the chest pain had stabilized.

Platelet malondialdehyde generation: Malondialdehyde was measured with the method of Smith et al.[12] and Stuart et al.[13] Blood was collected in buffered citrate anticoagulant (9:1 by volume). The platelet button, obtained by centrifugation at 600 *g* for 15 minutes, was incubated for 60 minutes at 37° C in a water bath as a 2.0 ml suspension containing phosphate-buffered saline solution and n-ethylmaleimide. After 60 minutes, the reaction was terminated by addition of 2.0 ml of 2.3 percent perchloric acid containing 0.53 percent 2-thiobarbituric acid. After agitation in a vortex mixer, the solution was heated for 15 minutes in a boiling water bath. The mixture was then cooled to room temperature and centrifuged, and the optical density of the supernatant pink chromogen

TABLE I

Extent of Coronary Artery Disease and Platelet Function in 22 Patients

Case	Age (yr)	CAD	Malondialdehyde (nmol/10^9 platelets)	PGI_2 for 50% Aggregation Inhibition (ng)	EMA for 50% Aggregation (ng)	Comments
			Group A Patients			
1	54	3VD	—	1.60	130	—
2	52	3VD	1.53	3.00	113	Repeated test: PGI_2 2.5, EMA 230
3	53	3VD	2.47	2.25	—	—
4	52	3VD	1.55	2.25	—	—
5	71	1VD	3.00	5.00	94	Repeated test: PGI_2 4.5, EMA 120
6	63	1VD	2.15	1.30	168	Repeated test: PGI_2 0.55 Patient had LAD spasm
7	59	3VD	—	7.30	—	—
8	57	—	—	2.20	123	—
9	55	3VD	2.15	1.15	111	Repeated test: PGI_2 1.15, EMA 112
10	46	2VD	5.14	3.50	180	Repeated test: PGI_2 3.5, EMA 190
Mean ± SEM	56	2.4VD	2.57	2.96	131	
	2	0.3	0.47	0.60	12	
			Group B Patients			
11	44	1VD	—	0.60	75	RCA spasm
12	53	—	0.97	0.65	160	—
13	55	3VD	—	0.88	113	—
14	70	3VD	—	0.55	140	—
15	57	3VD	—	0.88	—	—
16	57	—	1.41	1.00	—	—
17	60	3VD	3.67	1.00	122	Repeated test: unchanged
18	46	2VD	3.51	1.20	171	Repeated test: PGI_2 1.07
19	58	3VD	2.22	2.20	—	—
20	57	2VD	2.13	1.15	162	—
21	53	—	—	1.00	156	—
22	48	2VD	3.18	1.20	117	—
Mean	55	2.4	2.44	1.03	135	
± SEM	2	0.2	0.40	0.12	10	
(Group A + B)	55	2.4	2.51	1.90	133	
± SEM	1	0.2	0.30	0.30	8	

CAD = coronary artery disease (greater than 50 percent luminal narrowing) (1, 2, 3VD indicates 1, 2 or 3 vessel disease); EMA = cyclic endoperoxide analog; LAD = left anterior descending coronary artery; PGI_2 = prostacyclin; RCA = right coronary artery; SEM = standard error of the mean; — = procedure not done.

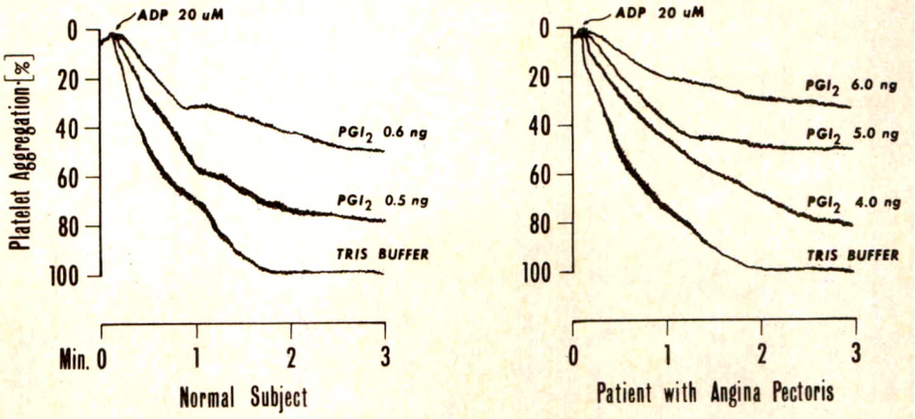


FIGURE 1. Platelet sensitivity to aggregation inhibitory actions of prostacyclin (PGI_2) in a normal subject (**left**) and in a patient with severe angina pectoris (**right**). Adenosine diphosphate (ADP), 20 μM, was used as the aggregation-stimulating agent. Tris buffer alone did not affect platelet aggregation. Platelets from the patient with angina pectoris required 5 ng of PGI_2 compared with 0.6 ng in the normal subject for a similar degree of platelet aggregation inhibition.

was read at 532 μ in a spectrophotometer. Malondialdehyde generation was expressed as nmol/10^9 platelets.

Sensitivity of platelets to prostacyclin: Platelet-rich plasma was obtained by centrifugation at 150 g for 8 minutes. The remaining blood was centrifuged at 5,000 g for 30 minutes to obtain platelet-poor plasma. Platelet counts in platelet-rich plasma were adjusted to 300,000 to 400,000/mm^3 by adding platelet-poor plasma. Platelet aggregation in response to addition of adenosine diphosphate (ADP) 20 μmol (0.05 ml) to 0.40 ml platelet-rich plasma and 0.05 ml Tris buffer was determined with measurement of light transmission in a Biodata aggregometer. ADP was kept as stock solution and diluted at the time of testing. Prostacyclin obtained as the sodium salt (Upjohn Co., Kalamazoo, Michigan) was diluted in freshly prepared Tris buffer to achieve different concentrations and stored at 0° C. Platelet-rich plasma (0.40 ml) and 0.05 ml of prostacyclin solution (final amounts 0.1 to 10.0 ng) were incubated at 37°C for 5 minutes in Siliconized cuvettes and constantly stirred before the addition of 20 μM of ADP. Different prostacyclin concentrations were used until the concentration that inhibited control platelet aggregation by 50 percent was obtained (Fig. 1).

Sensitivity of platelets to endoperoxide analog (EMA): (15 S)-hydroxy 11α, 9α-(epoxymethano) prosta-5Z, 13E-dienoic acid (EMA) (U-46619) (Upjohn Co., Kalamazoo, Michigan) was used to evaluate platelet sensitivity to its proaggregatory actions. EMA, a stable synthetic analog with biologic activities similar to those of prostaglandin endoperoxide and thromboxane A_2,[14] was dissolved in normal saline solution to achieve different concentrations and stored at room temperature. Platelet-rich and platelet-poor plasma was obtained as described; 0.05 ml of EMA solution was added to 0.45 ml platelet-rich plasma to determine the minimal concentration that produced 50 percent platelet aggregation (Fig. 2).

Data analysis: All data are expressed as mean ± standard error of the mean. Comparisons between patients with angina pectoris and control subjects were made using Student's t test for unpaired data. A probability (p) value of less than 0.05 was considered statistically significant.

Results

The data on patients, extent of coronary disease and platelet function are shown in Table I and Figure 3.

Platelet malondialdehyde generation: In control subjects, malondialdehyde production ranged from 0.72 to 2.17 nmol/10^9 platelets (mean 1.70 ± 0.13). In patients with angina pectoris as a group, malondialdehyde levels ranged from 0.97 to 5.14 nmol/10^9 platelets (mean 2.51 ± 0.30). This difference in malondialdehyde generation between normal subjects and patients with angina pectoris was significant ($p < 0.01$). In group A patients, the levels were similar to those of group B patients (2.57 ± 0.47 versus 2.44 ± 0.40 nmol/10^9 platelets, $p > 0.10$).

Sensitivity of platelets to prostacyclin: In control subjects, the amount of prostacyclin required to inhibit ADP-induced platelet aggregation by 50 percent ranged from 0.45 to 1.00 ng (mean 0.68 ± 0.05). Significantly larger amounts (range 0.55 to 7.3 ng, mean 1.90 ± 0.35

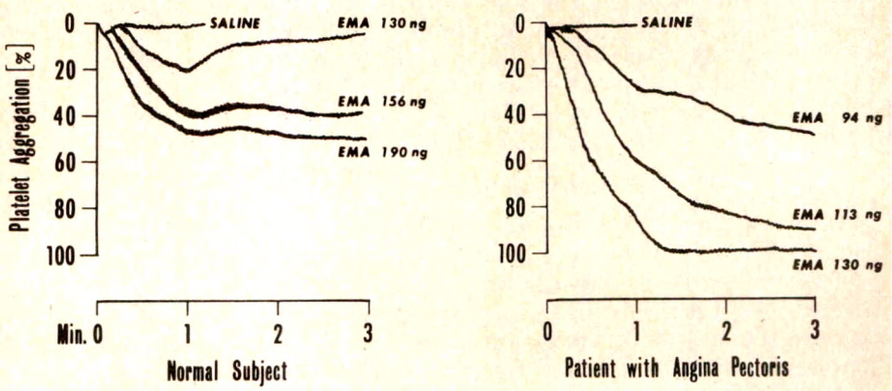


FIGURE 2. Platelet sensitivity to proaggregatory actions of epoxymethanodienoic acid (EMA) (endoperoxide analog) in a normal subject (**left**) and in a patient with severe angina pectoris (**right**). Platelets from the patient with angina pectoris required 94 ng of EMA compared with 160 ng in the normal subject (same subjects as in Figure 1).

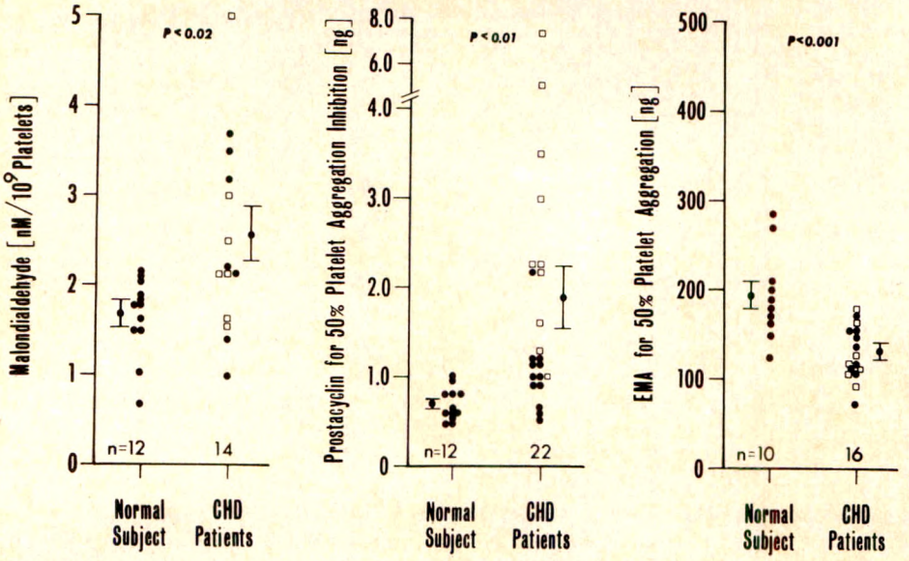


FIGURE 3. Platelet malondialdehyde generation (**left panel**), amount of prostacyclin for 50 percent platelet aggregation inhibition (**middle panel**) and amount of epoxymethanodienoic acid (EMA) for 50 percent platelet aggregation (**right panel**) in normal subjects and in patients with coronary heart disease (CHD) and angina pectoris. Group A patients are shown in **open squares** and group B in **closed circles.**

ng, $p < 0.01$) were required for similar degrees of inhibition in patients with angina pectoris. All but five patients with angina pectoris required 1.0 ng or more of prostacyclin for similar inhibition, whereas all but one of the control subjects required less than 1.0 ng of prostacyclin. There was no significant correlation between the extent of coronary artery disease and the platelet sensitivity to prostacyclin, but significantly more prostacyclin was required for platelet aggregation inhibition in group A patients, who were experiencing angina pectoris, than in group B patients, who had angina several hours earlier (2.96 ± 0.60 versus 1.03 ± 0.12 ng, $p < 0.005$). On a repeated test of platelet sensitivity to prostacyclin in five group A patients, less prostacyclin was required in three for similar degree of aggregation inhibition and similar amounts as during the anginal attack in the other two. In one of two group B patients with a repeated test, slightly less prostacyclin was required and in the other the same amount was required as in the first test.

Sensitivity of platelets to EMA: In control subjects, 50 percent platelet aggregation was observed with the addition of 125 to 285 ng (mean 194 ± 16) epoxymethanodienoic acid (EMA). In patients with angina pectoris as a group, significantly less ($p < 0.001$) EMA (range 75 to 180 ng, mean 133 ± 8) was required for a similar degree of aggregation. In group A patients, platelet sensitivity to EMA was similar to that in group B patients (131 ± 12 versus 135 ± 10 ng, $p < 0.10$). On a repeat test in four group A patients, all showed a reduction in enhanced platelet sensitivity to EMA.

Discussion

Platelets, prostaglandins and coronary artery disease: Although increased platelet aggregation has been demonstrated in patients with coronary artery disease[5,6,14–16] the mechanisms involved are not clear. The results of this study indicate that platelet prostaglandin generation is significantly greater in patients with angina pectoris than in normal subjects. In addition, in certain patients with ischemic heart disease, platelet sensitivity to proaggregatory effects of endoperoxide analog is increased, and that to antiaggregatory effects of prostacyclin is significantly diminished.

Platelet prostaglandin generation: This was evaluated by measuring malondialdehyde, which is an end product of metabolism of several prostaglandins including thromboxane A_2.[12,13] We found significantly increased malondialdehyde generation in patients with angina pectoris as a group than in normal subjects. However, there was no consistent relation between malondialdehyde levels and extent of coronary disease and time elapsed from the episode of angina pectoris before the blood sample was collected. Some patients whose blood was collected during an acute anginal episode had high malondialdehyde levels, whereas others had normal levels. These results are similar to those of Lewy et al.,[17] who measured the thromboxane A_2 degradation product, thromboxane B_2, in patients with coronary artery disease and found elevated thromboxane B_2 levels during pacing-induced ischemia. In another study,[14] augmented rates of conversion of arachidonic acid to thromboxane A_2 were demonstrated in certain patients with myocardial infarction. Increased platelet prostaglandin production in certain patients could account for enhanced platelet aggregation and vasoconstriction, which would be expected to limit blood flow in atherosclerotic coronary arteries. Although the mechanisms involved in increased production of platelet prostaglandins are not known, it has been shown that atherosclerotic and injured endothelium generates reduced amounts of prostacyclin.[18–20] This disturbed state of balance between vascular prostacyclin synthesis and platelet prostaglandin production may be related to vasoconstriction and enhanced platelet aggregation, resulting in the syndrome of myocardial ischemia in certain patients.

Platelet sensitivity to prostacyclin: Prostacyclin at concentrations of approximately 1.0 ng/ml effectively inhibits human platelet aggregation induced in vitro by

most agents.[21] In our studies in normal subjects, prostacyclin in similar amounts inhibited ADP-induced platelet aggregation. However, in patients with ischemic heart disease significantly higher amounts of prostacyclin were required for a similar degree of inhibition of platelet aggregation. Platelets from patients whose blood was collected during episodes of angina pectoris had significantly lower sensitivity to prostacyclin compared with other patients who had chest pain several hours earlier. Whether platelets become acutely less sensitive to prostacyclin before or during an episode of chest pain is not known. In five patients we repeated testing of sensitivity to prostacyclin several hours after the acute episode of angina pectoris. Although slightly smaller amounts of prostacyclin were required for inhibition of platelet aggregation in three of the five patients, platelet sensitivity to prostacyclin was still found to be greatly diminished compared with sensitivity in control subjects. It is also possible that certain metabolic products of ischemia render platelets acutely less sensitive to actions of prostacyclin.

Lack of correlation between extent of coronary disease and platelet sensitivity to prostacyclin (Table I) suggests that the presence of atherosclerosis alters platelets. Reduced sensitivity of platelets to prostacyclin coupled with diminished prostacyclin generation by atherosclerotic vessels[18–20] may be expected to lead to intravascular platelet thrombus formation and impede blood flow. An acute alteration in platelet sensitivity to prostacyclin by some as yet unkown cause may be a mechanism for the acute episode of angina pectoris.

Platelet sensitivity to endoperoxide analog: Increased sensitivity of platelets from patients with coronary artery disease to the proaggregatory actions of vasoconstrictor prostaglandin as observed in our study may be detrimental, because smaller quantities of thromboxane A_2 may be adequate for platelet thrombus formation and vasoconstriction, resulting in the syndrome of angina pectoris. These studies support the observations of Szczeklik et al.,[14] who demonstrated that less endogenous thromboxane A_2 is required to induce aggregation in patients with angina pectoris than in control subjects. This increase in platelet sensitivity to vasoconstrictor prostaglandin in the presence of evidence for increased platelet prostaglandin generation could be an important mechanism in the pathogenesis of myocardial ischemia.

Pathophysiologic implications: Similar alterations in prostaglandin generation and platelet sensitivity to platelet-active prostaglandins may be responsible for the syndromes of variant angina pectoris (coronary arterial spasm)[1–3] and myocardial ischemia with normal coronary arteries.[22] Indeed, in a preliminary study, Lewy et al.[23] demonstrated elevated thromboxane B_2 activity in patients with coronary arterial spasm. Although no studies on platelet function in subjects with normal coronary arteries and myocardial ischemia are available, the possibility of transient luminal obstruction by platelet plugs has been suggested.[4] Our observations of enhanced prostaglandin generation by platelets and abnormal platelet sensitivity to prostacyclin and endoperoxide analog in patients with angina pectoris may have important pathophysiologic implications.

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Electrophysiologic and Hemodynamic Studies in Patients Resuscitated From Cardiac Arrest

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Fifty-two patients resuscitated from cardiac arrest underwent electrophysiologic studies. The earliest documented arrhythmia at the time of initial or recurrent (18 patients) cardiac arrest was ventricular fibrillation (30 patients) or ventricular tachycardia (20 patients); in 2 patients no arrhythmia was documented before defibrillation. Programmed ventricular stimulation revealed inducible arrhythmias in 33 patients (63 percent). Of the 30 patients with ventricular fibrillation as the initial arrhythmia, 13 had inducible arrhythmias—ventricular fibrillation (4 patients), sustained ventricular tachycardia (6 patients) and nonsustained ventricular tachycardia (3 patients). In the 20 patients with ventricular tachycardia as the initial arrhythmia, sustained ventricular tachycardia was initiated in 17 patients and torsade de pointes in 1. Patients with inducible arrhythmias had longer mean A-H and H-V intervals than those without inducible arrhythmias (91.1 versus 76.6 ms and 62.5 versus 50.3 ms, respectively). Prolonged H-V intervals (17 of 33) and intraventricular conduction defects (18 of 33) were more common in patients with than in those without inducible arrhythmias (4 of 19 and 7 of 19, respectively). Mean cardiac index was lower (2.4 versus 3.9 liters/min per m^2), left ventricular end-diastolic pressure higher (17.0 versus 9.4 mm Hg), and ejection fraction lower (36.1 versus 57.2 percent) in the group with inducible arrhythmias than in those in whom no arrhythmia could be induced. These data suggest that (1) ventricular tachycardia often precipitates cardiac arrest; and (2) electrophysiologic testing may provide data on which to base therapy in patients resuscitated from cardiac arrest.

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Cardiac arrest is usually secondary to ventricular tachycardia or fibrillation.[1–6] Although most of these arrhythmias are presumed to be secondary to ischemia with or without infarction, they can occur in patients without any cardiac disease.[2,7] Thus, acute ischemia cannot explain all such events. Moreover, no arrhythmia appears to be a specific predictor of sudden death. As a result, empiric antiarrhythmic therapy directed toward suppressing nonspecific arrhythmic markers has not proved successful in preventing recurrent cardiac arrest.[3,8–10] This study was undertaken: (1) to evaluate the hemodynamic and electrophysiologic characteristics of patients resuscitated from cardiac arrest secondary to ventricular tachycardia or fibrillation, or both; and (2) to determine whether a potentially lethal electrophysiologic milieu could be recognized, thus providing the physician with a marker toward which pharmacologic or surgical therapy, or both, might be aimed.

Methods

Study patients: Electrophysiologic studies were performed in 52 patients who were resuscitated from cardiac arrest. In 32 instances the initial hospitalization was at the Hospital of the University of Pennsylvania. The remaining 20 patients were initially hospitalized elsewhere and were subsequently referred to this hospital.

To enter the study patients were required to (1) have no acute myocardial infarction in the immediate postarrest period, (2) be in hemodynamically and electrophysiologically stable condition for at least 48 hours, and (3) give informed written consent. There were 40 men and 12 women ranging in age from 21 to 75 years (Table I). Organic heart disease was clinically present in 47 patients, coronary artery disease being most frequent (37 patients). Five patients had no prior history of cardiac disease.

All patients were admitted to a coronary intensive care unit for 2 to 5 days after resuscitation to rule out myocardial infarction and begin therapy. Myocardial infarction was defined by two of the following: (1) new diagnostic Q waves, (2) a rise of 150 percent in serum cardiac enzymes, or (3) a history of prolonged chest pain with persistent (longer than 72 hours) T wave inversions. In addition to constant monitoring in the intensive care unit, all 32 patients initially admitted to the Hospital of the University of Pennsylvania were maintained on computerized telemetry for 24 to 48 hours and all 52 patients underwent at least one 24 hour electrocardiographic Holter monitoring before the electrophysiology study.

Features of cardiac arrest: The initial cardiac arrest occurred outside the hospital in 42 patients and in the hospital in 10 patients. All 10 in-hospital cardiac arrests were *sudden* and *unexpected* in patients who were in clinically stable condition. Four occurred 14 to 21 days after uncomplicated myocardial infarction in the absence of any precipitating factor (exercise or angina, for example). There was no evidence of recurrence or extension of infarction in any of these patients. The *onset* of 6 of the 10 in-hospital cardiac arrests was monitored and revealed ventricular tachycardia in 3 patients and ventricular fibrillation in 3. The remaining patients had ventricular fibrillation at the time of resuscitation, which was within 3 minutes of cardiovascular collapse.

TABLE I

Clinical Cardiac Diagnosis in 52 Patients With Cardiac Arrest

Coronary artery disease	37	
Myocardial infarction		29
Cardiomyopathy	2	
Mitral valve prolapse	3	
Coronary arterial spasm	1	
Valvular heart disease	2	
Hypertensive cardiovascular disease	2	
No heart disease	5	
Total	52	

The arrhythmia recorded at the time of initial resuscitation was ventricular fibrillation in 44 patients and ventricular tachycardia in 6 patients; and in 2 it was not documented before cardioversion. Eighteen patients whose initial cardiac arrest occurred outside the hospital had a new cardiac arrest in the hospital where onset was electrocardiographically monitored. The new arrest occurred 5 to 52 days after stabilization after the initial episode. The rhythm at the onset of the monitored arrest was ventricular fibrillation in 4 patients (Fig. 1) and ventricular tachycardia with or without degeneration to ventricular fibrillation in 14 (Fig. 2 and 3). Two of the monitored cardiac arrests were clearly precipitated by drugs—one by disopyramide (Fig. 1) and one by procainamide. No drug, drug interaction or electrolyte imbalance could be implicated in the remaining patients. Overall, the earliest rhythm disturbance noted during the initial or recurrent cardiac arrest was ventricular fibrillation in 30 patients and ventricular tachycardia in 20 patients (Table II).

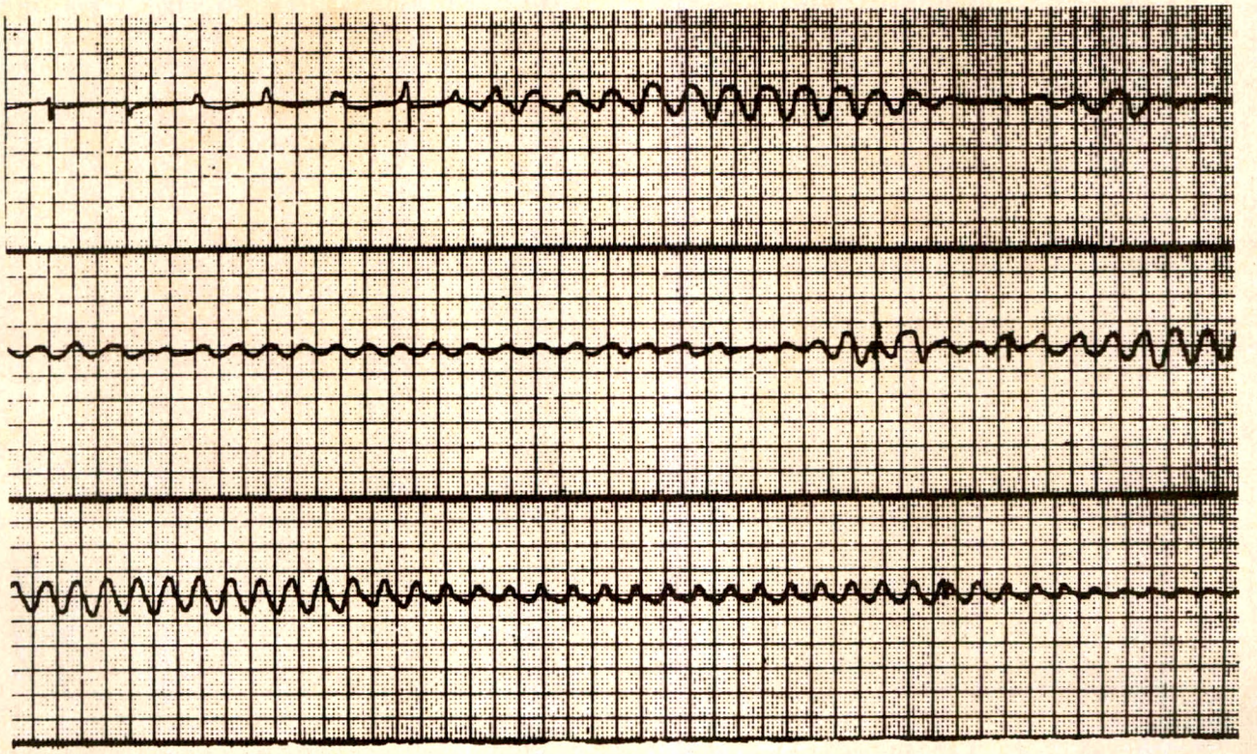


FIGURE 1. Recurrent cardiac arrest due to ventricular fibrillation. Ventricular fibrillation is initiated by four ventricular premature depolarizations with long interectopic intevals. This recording was obtained from a modified V_1 lead during telemetry.

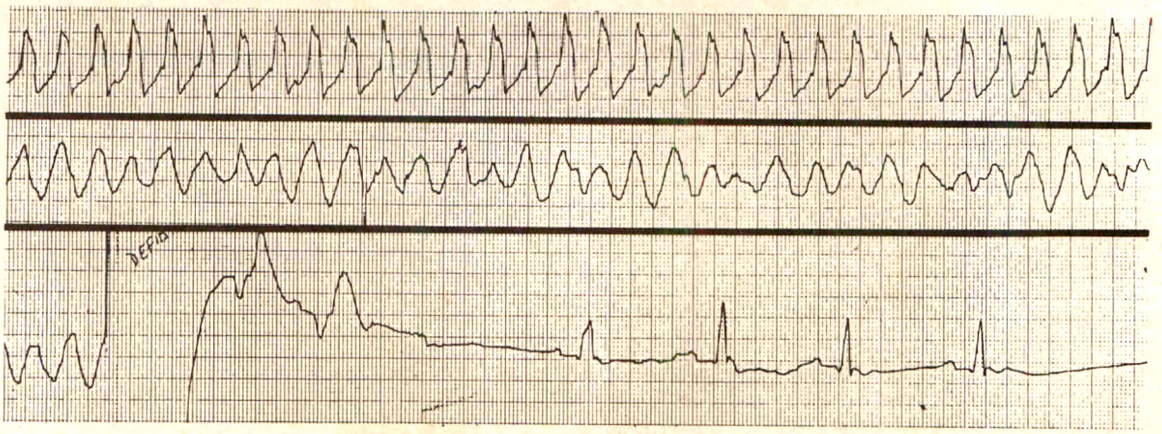


FIGURE 2. Cardiac arrest due to ventricular tachycardia degenerating into ventricular fibrillation. A modified lead I was recorded in the coronary care unit. Cardiac arrest is initiated by an episode of sustained ventricular tachycardia at a rate of 170/min (**top panel**), that degenerates to ventricular fibrillation (**middle panel**). Electrical defibrillation results in sinus rhythm (**bottom panel**). Note the presence of an intraventricular conduction defect during sinus rhythm.

Electrophysiologic studies: All patients underwent electrophysiologic studies 5 to 60 days after cardiac arrest. All antiarrhythmic agents were discontinued 24 to 48 hours before the study. Two to four electrode catheters were passed percutaneously into the right or left, or both, femoral veins or into the antecubital fossa, or both areas, and positioned at the high right atrium, His bundle recording site and right ventricular apex. An additional catheter was placed in the coronary sinus in 36 patients. Sinus node function, atrioventricular condition times and response to ventricular stimulation were tested. Our ventricular stimulation protocol had previously been reported[11] and in all patients consisted of the delivery of one or two ventricular extrastimuli during sinus rhythm or paced ventricular rhythm from the right ventricular apex. The coupling intervals of the stimuli were decreased until both encountered ventricular refractoriness. Rapid ventricular pacing at cycle lengths of 400 to 250 ms was also performed for 10 to 60 seconds. In 22 patients right ventricular stimulation failed to initiate a sustained ventricular tachyarrhythmia, and in each left ventricular stimulation was used. The stimulation protocol from the left ventricle was the same as that from the right. The intracardiac electrograms were displayed simultaneously with two to three surface electrocardiographic leads on a multichannel oscilloscope (Electronics for Medicine DR16 or VR16) and stored on magnetic tape (Honeywell 5600C) for subsequent retrieval. All equipment was isolated from the patients and leakage current was minimal, ranging from 2 to 6 μamperes.

Results

Clinical and electrocardiographic findings: Twenty-eight patients gave a history of myocardial infarction before cardiac arrest. In four patients cardiac arrest occurred 2 to 3 weeks after acute myocardial infarction and in 24 patients more than 2 months after infarction. The electrocardiographic findings on admission revealed myocardial infarction in 21 patients; the infarction was anterior in 15. Intraventricular conduction defects, present in 25 patients (48 percent), included right bundle branch block in 8, left bundle branch block in 10, nonspecific intraventricular conduction defect in 5 and left anterior hemiblock in 2 patients. All but one patient with an intraventricular conduction disturbance had known cardiac disease.

During the 24 to 48 hours after the initial cardiac arrest, almost all patients manifested some ventricular arrhythmia in the coronary care unit. Complex arrhythmias (ventricular premature depolarizations with a frequency greater than 300/h, couplets or triplets averaging more than 10/h, or ventricular tachycardia) were documented in 18 patients, noncomplex ventricular arrhythmias in 30 patients, and no ventricular arrhythmias in 4 patients. Complex ventricular arrhythmias were observed in 7 of the 18 patients with a re-

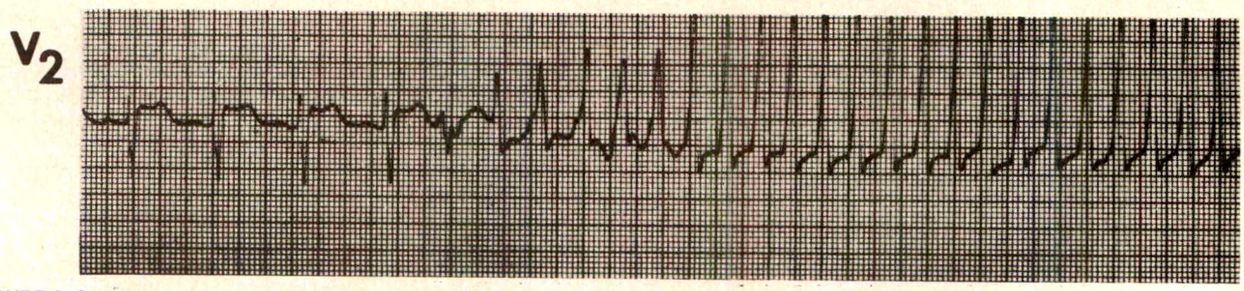


FIGURE 3. Cardiac arrest initiated by rapid sustained ventricular tachycardia. The tracing is from a modified V_2 lead during telemetry. A rapid ventricular tachycardia (cycle length 240 ms) is initiated with a ventricular premature depolarization occurring after the T wave (coupling interval 400 ms). This resulted in a cardiac arrest during which the rhythm remained ventricular tachycardia.

current cardiac arrest and in 11 of 34 without a recurrence (difference not significant). Intraventricular conduction disturbances were observed in 10 (71 percent) of 14 patients with recurrent cardiac arrest initiated by ventricular tachycardia and in none of the 4 patients whose recurrent arrest was due to primary ventricular fibrillation.

Electrophysiologic studies: The results of ventricular stimulation depended on the mechanism of cardiac arrest (Fig. 4). In 30 patients the earliest arrhythmia recorded at the time of initial or recurrent cardiac arrest was ventricular fibrillation. In this group of patients programmed stimulation initiated ventricular tachyarrhythmias in only 13 patients. In four patients ventricular fibrillation was induced, in five patients ventricular tachycardia degenerating into ventricular fibrillation was induced, in one patient sustained ventricular tachycardia was induced, and in three patients nonsustained ventricular tachycardia was induced. Among the remaining 17 patients a single repetitive ventricular response was noted in 5 and no repetitive response in 12.

In 20 patients ventricular tachycardia with or without degeneration into ventricular fibrillation was documented as the mechanism of the tachycardia. In 17 (85 percent) of these patients sustained ventricular tachycardia was induced, and in 2 of the 17 it degenerated into ventricular fibrillation. In one patient a polymorphic ventricular tachycardia typical of torsade de pointes was induced. Therefore, in 18 (90 percent) of 20 of the patients with ventricular tachycardia as the initiating mechanism for cardiac arrest, a ventricular tachyarrhythmia could be induced by programmed stimulation. Five patients with induced sustained ventricular tachycardia required cardioversion because of acute hemodynamic deterioration, whereas in the remainder the arrhythmia could be terminated by programmed stimulation. There were no cardiac or neurologic sequelae in any of the patients who required cardioversion.

In the two patients whose arrhythmia at the time of cardiac arrest was not documented, ventricular tachyarrhythmias were induced by programmed stimulation. Sustained ventricular tachycardia was induced in both of these patients, in one of whom degeneration into ventricular fibrillation occurred. Thus, in 33 (63 percent) of the 52 patients a ventricular tachyarrhythmia was induced by programmed stimulation.

The A-H and H-V intervals were significantly different in patients with and without inducible ventricular arrhythmias (Fig. 5 and 6). Patients with inducible arrhythmias demonstrated longer mean A-H (91.1 versus 76.6 ms, $p < 0.005$) and H-V (62.5 versus 50.3 ms, $p < 0.01$) intervals than did those without inducible ven-

TABLE II

Results of Ventricular Electrical Stimulation

Earliest Rhythm Recorded at Cardiac Arrest	Cases (n)	Induced Rhythm	Cases (n)	
VF	30	VF	4	
		Sustained VT	6	
		Degeneration to VF		5
		Nonsustained VT	3	
VT	20	Sustained VT	17	
		Degeneration to VF		2
		Nonsustained VT	1	
None	2	Sustained VT	2	
		Degeneration to VF		
Total	52		33	7

VF = ventricular fibrillation; VT = ventricular tachycardia.

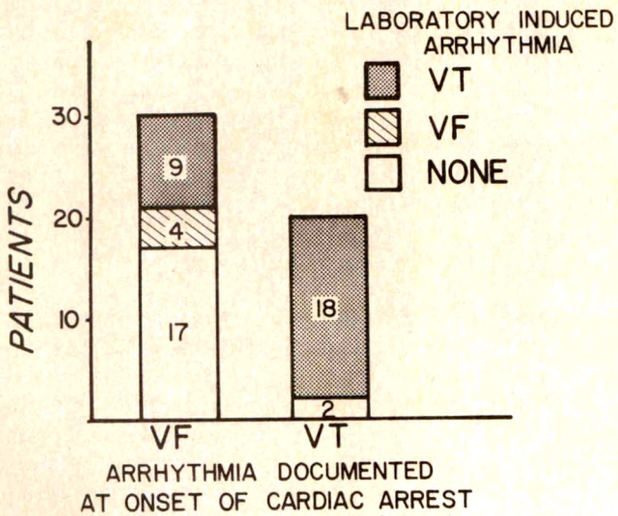


FIGURE 4. Results of programmed ventricular stimulation in patients with previous cardiac arrest. The incidence of induced ventricular arrhythmias is shown in relation to the earliest recorded rhythm during cardiac arrest. VF = ventricular fibrillation; VT = ventricular tachycardia.

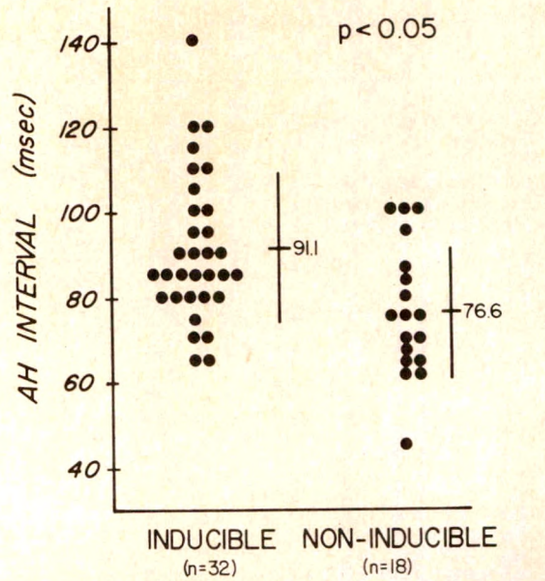


FIGURE 5. A-H intervals in patients with and without inducible arrhythmias.

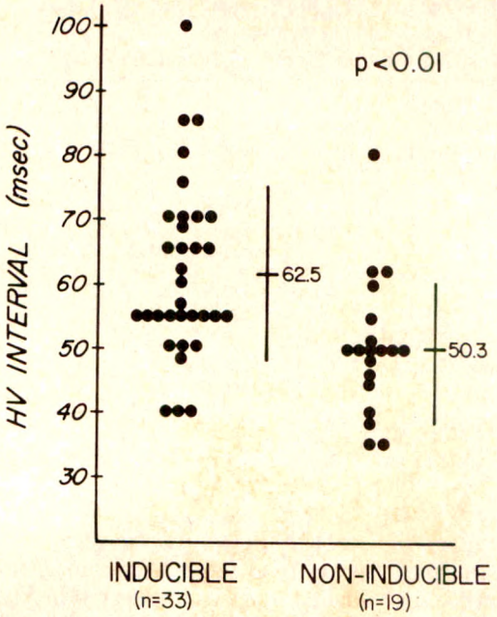


FIGURE 6. H-V intervals in patients with and without inducible arrhythmias.

tricular arrhythmias. Seventeen patients with inducible arrhythmias had a prolonged H-V interval (greater than 55 ms) versus 4 patients without inducible ventricular tachyarrhythmias ($p < 0.001$). Atrioventricular (A-V) nodal refractory periods (260 to 390 ms) and paced cycle length to A-V nodal Wenckebach conduction (300 to 500 ms) were normal in all 50 patients so studied (2 patients had atrial fibrillation). Sinus nodal function was normal in all but 1 of 46 patients tested.

TABLE III

Results of Cardiac Catheterization

	Range	Mean
Hemodynamics		
LVEDP (mm Hg)	4–30	14.5
CI (liters/min per m^2)	1.5–4.6	2.6
EF (%)	20–80	43
Coronary angiography		
Coronary artery disease (number of patients)		32
1 VD		6
2 VD		11
3 VD		15
Coronary arteries with >50 percent obstruction (number of patients)		
LAD		26
RCA		24
LCx		21
Left Ventriculography (number of patients)		
Normal		13
Isolated segmental abnormalities		17
Diffuse abnormalities		12
LV aneurysm		16

CI = cardiac index; EF = ejection fraction; LAD = left anterior descending artery; LCx = left circumflex coronary artery; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; 1, 2 and 3 VD = one, two and three vessel coronary artery disease; RCA = right coronary artery.

Although electrocardiographic intraventricular conduction disturbances were common in both groups, they were more common in patients with (18 of 32) than in those without (7 of 19) inducible arrhythmias. Electrocardiographic evidence of old or new myocardial infarction was more common in patients with inducible arrhythmias—16 of 33 versus 5 of 19 patients. In two of the five patients without cardiac disease, ventricular tachycardia that degenerated into ventricular fibrillation was induced; no arrhythmia was induced in the other three patients.

Hemodynamic-angiographic correlates of electrophysiologic testing: Forty-two patients underwent cardiac catheterization, including 28 with and 14 without inducible ventricular arrhythmias (Table III). The 10 patients who refused cardiac catheterization did not differ clinically from those who underwent catheterization. In the patients in whom ventricular tachycardia or fibrillation was induced in the laboratory, cardiac catheterization revealed more marked impairment of hemodynamic function and more severe coronary disease (Fig. 7 and 8). Mean cardiac index was lower (2.4 versus 3.9 liters/min-m^2; difference not significant), left ventricular end-diastolic pressure higher (17.0 versus 9.4 mm Hg; $p < 0.001$), and ejection fraction lower (36.1 versus 57.2 percent ; $p < 0.008$), in the group with inducible arrhythmias than in those in whom no arrhythmia could be induced.

Coronary artery disease was present in 23 of 28 patients with inducible arrhythmias. Two of these patients had one vessel disease, 9 had two vessel disease and 12 had three vessel disease (Fig. 8). The remaining five patients with inducible arrhythmias included one with cardiomyopathy, one with mitral valve prolapse and one with rheumatic heart disease; two patients had no heart disease. In the group of 14 patients in whom no ventricular tachyarrhythmia was inducible, coronary artery disease was present in 9 patients, including 4 with one vessel, 2 with two vessel and 3 with three vessel disease. The remaining patients without inducible arrhythmias included one patient with cardiomyopathy, one patient with normal coronary arteries but coronary arterial spasm and three patients without heart disease. Left ventricular aneurysm was present in 14 patients with inducible arrhythmias and in only 2 in whom no arrhythmia could be induced.

Discussion

Ventricular fibrillation versus ventricular tachycardia as initiating arrhythmia of cardiac arrest: Ventricular fibrillation has been considered to be the mechanism of death in most patients who die suddenly, primarily because it is the most frequent arrhythmia recorded at the time of attempts at resuscitation.[1–6] However, the initiating arrhythmia is rarely recorded; thus, the primary arrhythmia resulting in ventricular fibrillation is not established. We were able to monitor the onset of cardiac arrest in 24 patients, including 6 of 10 patients who had the initial cardiac arrest in the hospital, and 18 patients with a new arrest during monitoring. All of these patients were in clini-

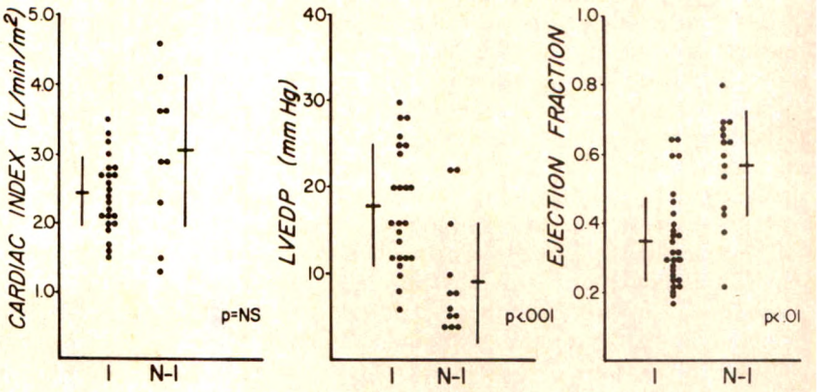


FIGURE 7. Cardiac function in patients with (I) and without (N-I) inducible ventricular tachyarrhythmias, as reflected by cardiac index, left ventricular end-diastolic pressure (LVEDP) and ejection fraction.

cally stable condition at the time of the cardiac arrest, which was a sudden and unexpected event. Of note was the large incidence of ventricular tachycardia as the initiating mechanism for cardiac arrest. Although the frequency of ventricular tachycardia as the initiating arrhythmia seems high, previous studies in several laboratories[11–13] have demonstrated that ventricular tachycardia commonly produces hemodynamic collapse or degenerates to ventricular fibrillation, or both.[11–13] In our experience this occurs about 20 percent of the time,[11,12] and probably would occur more often if programmed stimulation were not available to terminate the arrhythmia. An obvious additional factor is that patients with cardiac arrest precipitated by ventricular tachycardia appear to be those most likely to survive.[3,5] Thus our patient group was selected.

Ventricular tachycardia induced by programmed electrical stimulation: the responsible mechanism of cardiac arrest? The fact that in this study recurrent cardiac arrest was frequently initiated by ventricular tachycardia does not prove that this mechanism was responsible for the initial event in these patients. However, the circumstances of the new cardiac arrest (that is, sudden and unexpected in a patient in stable condition) suggest that the same arrhythmia was responsible for both events. Moreover, in the study we were able to induce ventricular tachycardia by programmed electrical stimulation in 90 percent of patients who had that arrhythmia. In our experience and that of others,[11–17] initiation of ventricular tachycardia by programmed electrical stimulation is a very specific indicator of its clinical occurrence. We[16] recently demonstrated that sustained ventricular tachycardia was *never* induced by the introduction of single or double ventricular extrastimuli or rapid ventricular pacing in a group of more than 400 patients who did not spontaneously exhibit the arrhythmia. We therefore believe that the initiation of ventricular tachycardia in patients resuscitated from cardiac arrest further supports the hypothesis that ventricular tachycardia is often the initiating mechanism of cardiac arrest. The mechanism of degeneration of ventricular tachycardia to ventricular fibrillation may be related to: (1) ischemia caused by decreased coronary perfusion and increased myocardial oxygen requirement, which in turn are secondary to hypotension and increased rate; or (2) rapid ventricular rates and irregular activation patterns that, unrelated to ischemia, can also result in ventricular fibrillation; or (3) both factors.

Patients with no inducible tachyarrhythmias: The initiating mechanism of the cardiac arrest in the 19 patients in whom no ventricular tachyarrhythmias were induced remains uncertain. Because this group included patients with and without coronary disease, transient ischemia cannot be implicated as the mechanism of the arrhythmia in these cases. The relative incidence of primary ventricular fibrillation versus that secondary to ventricular tachycardia is unknown. Perhaps more sophisticated stimulation techniques might have permitted replication of the arrhythmia in the remaining 19 patients.

Comparison with previous studies: Previously, Myerburg et al.[18] were able to induce ventricular tachycardia in five of six patients resuscitated from cardiac arrest in whom ventricular tachycardia was the initial rhythm documented. No arrhythmia could be induced in the remaining four patients in whom ventricular fibrillation was the initial rhythm recorded. These investigators therefore concluded that cardiac arrest in the latter group was due to transient ischemia and that electrophysiologic testing would not be worthwhile in most patients when performed 72 hours or more after cardiac arrest.

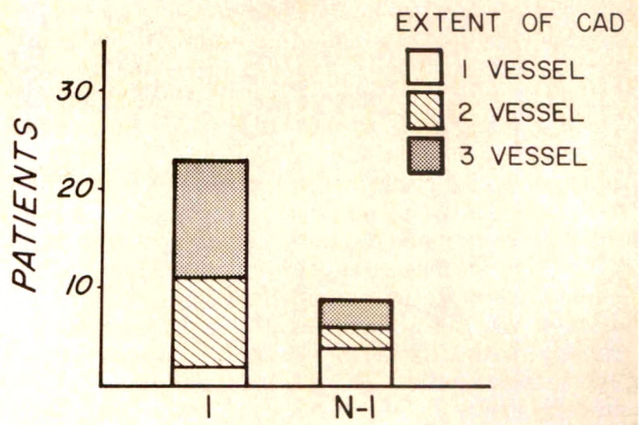


FIGURE 8. Extent of coronary artery disease (CAD) in patients with (I) and without (N-I) inducible ventricular tachyarrhythmias.

In our study we demonstrated a greater incidence of induction of ventricular tachycardia or fibrillation, or both. Although we apparently had a larger group of patients with ventricular tachycardia than did Myerburg et al., only six of our patients had ventricular tachycardia documented at the time of the *initial arrest*. It was only by monitoring recurrences in the hospital that we observed the frequent initiation of cardiac arrest by ventricular tachycardia. Thus, when the initial arrhythmias documented by the paramedics are compared, 6 of 10 patients studied by Myerburg et al. had ventricular tachycardia (5 of whom had inducible ventricular tachycardia), whereas, only 6 of 50 patients in our study had ventricular tachycardia documented during the first arrest. Therefore, the incidence of ventricular tachycardia recorded at the initial arrest in our patients was actually less than that in the study of Myerburg et al.

We believe that the difference in the frequency of induction of sustained ventricular arrhythmia was more likely due to the stimulation techniques used than to differences in patient population. Myerburg et al.[18] used only single ventricular stimuli at a single cycle length. Our stimulation protocol was more rigorous and included the use of single and double ventricular stimuli from multiple sites within the right ventricle and left ventricle (22 patients) at different drive cycle lengths and rapid pacing. Only after these perturbations failed to initiate a tachyarrhythmia did we consider the arrhythmia responsible for cardiac arrest noninducible.

Hemodynamic and electrophysiologic correlates: The hemodynamic and angiographic patterns in our patients were not different from those of patients in other studies of sudden cardiac death.[18–21] The vast majority of patients had coronary artery disease with a distribution of diseased vessels similar to those previously reported for both patients with sudden cardiac arrest and those with symptomatic coronary artery disease. In all instances, patients with two and three vessel disease predominated. However, patients with inducible arrhythmias appeared to have greater hemodynamic and angiographic ventricular dysfunction than did patients in whom arrhythmia could not be induced. In addition, our 33 patients with inducible malignant ventricular arrhythmias had a greater incidence of left ventricular aneurysm than did those with noninducible arrhythmias. This finding is not unexpected, because we demonstrated a large incidence of left ventricular aneurysm in patients with inducible recurrent sustained ventricular tachycardia.[11,22] Myerburg et al.[18] noted a similar large incidence of ventricular aneurysm in the patients whose cardiac arrest was caused by ventricular tachycardia and in whom the arrhythmia could be induced by programmed stimulation. This fixed substrate may account for the inducibility of the arrhythmia by programmed stimulation at any time independent of ischemia or other transient pathophysiologic effects.

As in most studies, the majority of our patients with coronary artery disease had a prior myocardial infarction, which was anterior in more than half.[2–7] We also observed a large incidence of intraventricular conduction defects (48 percent), a finding previously observed by other investigators.[3,4] Patients with inducible arrhythmia had greater impairment of hemodynamic function as well as more severe coronary disease. In addition, they had a higher proportion of abnormalities of atrioventricular conduction (that is, longer A-H and H-V intervals than did patients without inducible arrhythmias). All patients had antiarrhythmic therapy discontinued before the study; thus drug effects could not be implicated. These data suggest that those patients in whom ventricular tachyarrhythmias are inducible are more likely to have a fixed anatomic or physiologic milieu, or both, that permits induction of the arrhythmia by programmed stimulation.

Therapeutic implications: The empiric use of antiarrhythmic drugs to prevent sudden death has not met with great success. In fact, such therapy may precipitate cardiac arrest as it did in two of our patients. At the time of cardiac arrest 30 to 80 percent of patients are on empiric therapy.[3,8–10] This lack of success most likely results from the incorrect choice of antiarrhythmic agent, inadequate dosage, poor patient compliance, or all three. Recently, programmed stimulation has been used to predict drug therapy in patients in whom ventricular tachycardia can be reproducibly initiated.[12,13,15,17,23] Therapy (agent and dosage) chosen by such testing has proved effective in the long-term management of this arrhythmia. The fact that ventricular tachycardia or fibrillation, or both, could be reproducibly initiated in the laboratory in 63 percent of our patients suggests that programmed stimulation could be used to develop pharmacologic therapy in a fashion similar to that previously shown to be effective in the treatment of chronic recurrent sustained ventricular tachycardia. We[23] have been able to develop successful therapy for 13 patients in this manner, and have recently reported the preliminary results.

In patients whose cardiac arrest is secondary to ventricular tachycardia and in whom drugs fail, localization of the origin of ventricular tachycardia by endocardial mapping can be used to guide surgical therapy for these arrhythmias. This approach, when coupled with intraoperative mapping to guide surgical therapy, has been successfully used to ablate recurrent sustained ventricular tachycardia in patients whose anatomy is comparable with that of our patients who have had a cardiac arrest.[24–26] We therefore believe that programmed ventricular stimulation and endocardial mapping can play an important role in treatment of these patients for the prevention of recurrent cardiac arrest. Long-term follow-up studies using these techniques will be necessary to further establish the benefits of this approach.

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Amount of Narrowing by Atherosclerotic Plaque in 44 Nonbypassed and 52 Bypassed Major Epicardial Coronary Arteries in 32 Necropsy Patients Who Died Within 1 Month of Aortocoronary Bypass Grafting

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In 32 necropsy patients who died within 30 days of an aortocoronary bypass operation performed for relief of angina pectoris, the lumens in 42 (95 percent) of 44 nonbypassed and in 52 (100 percent) of 52 bypassed arteries were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque. Of 616 five mm segments of the 44 nonbypassed arteries examined histologically, 292 (47 percent) were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque; of 728 segments examined in the 52 bypassed arteries, 375 (52 percent) were similarly narrowed. Thirty-two (73 percent) of the 44 nonbypassed coronary arteries (in 23 patients) had been judged to be narrowed 50 percent or less in diameter on preoperative coronary angiography, but at necropsy 31 (97 percent) of these arteries were narrowed 76 to 100 percent in cross-sectional area and the other artery was narrowed 51 to 75 percent. Thus, significant amounts of atherosclerotic plaque tend to be present at necropsy in all three major coronary systems of patients with angina pectoris who die early after an aortocoronary bypass operation.

In patients undergoing aortocoronary bypass operations, one, two or three or more bypass conduits are inserted. The decision to bypass one major coronary artery and not another is usually determined by the degree and location of the narrowing or the size of the coronary artery on preoperative angiography. The accuracy of angiographic judgment or the status of the nonbypassed coronary artery has, to our knowledge, not been evaluated at necropsy in patients who died early after aortocoronary bypass operations. Thus, 44 nonbypassed coronary arteries were examined in 32 necropsy patients who died within 30 days of an aortocoronary bypass operation carried out for relief of angina pectoris, and the observations on the nonbypassed arteries were compared with those on the bypassed arteries.

Methods

Study patients: In the Pathology Branch of the National Heart, Lung, and Blood Institute, from 1972 through July 1979, we examined at necropsy the hearts of 117 patients who died after aortocoronary bypass procedures; 75 patients (64 percent) died within 60 days of the operation and 42 (36 percent) died later. Of the 75 patients who died within 60 days of operation, 43 (57 percent) had three or more aortocoronary bypass conduits inserted. The remaining 32 patients, all of whom died within 30 days of the bypass operation, had one (13 patients) or two (19 patients) bypass conduits inserted. This paper concerns only the latter 32 patients, whose ages ranged from 34 to 70 years (mean 55); 22 were men and 10 were women. All 32 patients had angina pectoris preoperatively, which was stable in 6 (19 percent) and unstable in 26 (81 percent). (Unstable angina pectoris was defined as anterior thoracic pain of recent onset [less than 1 month before clinical evaluation] or a recent change in the pattern of the pain

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in terms of frequency, severity, intensity and ease of provocation. Nocturnal angina or angina at rest or prolonged angina within 3 months of death was considered unstable.)

In addition to coronary heart disease, six patients (all with stable angina pectoris) also had valvular heart disease: isolated aortic-valve stenosis in two, isolated mitral stenosis in one, pure mitral regurgitation secondary to papillary muscle dysfunction in one and combined aortic and mitral stenosis in two. These six patients also had replacement of the mitral or aortic valve, or both, with a prosthesis in addition to the aortocoronary bypass procedure. In these six patients with associated valvular heart disease, 12 of the 18 major coronary arteries received a bypass conduit, or one major coronary artery was not bypassed in each. Excluding the 6 patients with associated valvular heart disease, none of the other 26 patients had had clinical evidence of congestive cardiac failure and none of the total 32 patients had had a clinical event compatible with acute myocardial infarction. However, at necropsy 4 of the 32 patients had one or more transmural left ventricular scars, and 7 other patients had relatively small subendocardial foci of left ventricular necrosis.

Eighteen of the 32 patients died in the operating room because of inability to be separated from cardiopulmonary bypass. The remaining 14 patients died after varying periods of shock (low cardiac output syndrome). The interval from the end of the operation to death in these 14 patients ranged from 2 hours to 24 days; in 4 patients, 12 hours or less; in 3 patients, from 16 to 24 hours; in 4 patients, from 2 to 4 days; and in 3 patients, from 6, 14 and 24 days, respectively. None of the 18 patients who died in the operating room had left ventricular myocardial necrosis detected histologically at necropsy. Of the remaining 14 patients who died later, 4 had one or more foci of left ventricular myocardial necrosis (that is, acute myocardial infarction) at necropsy.

Examination of coronary arteries: This report focuses on the status of the 44 major nonbypassed and the 52 bypassed epicardial coronary arteries in the 32 patients. The major arteries analyzed were the right, left anterior descending and left circumflex (Table I). However, if a conduit had been

TABLE I

Summary of Coronary Arterial Findings in 32 Patients With Angina Pectoris Who Died Within 30 Days of Aortocoronary Bypass

Nonbypassed coronary arteries		
Left anterior descending (LAD) only	1	20 patients (single artery)
Left circumflex (LCx) only	9	
Right (RCA) only	10	
LAD and LCx	2	12 patients (two arteries)
LAD and RCA	1	
LCx and RCA	9	
Nonbypassed coronary arteries and (number of arteries) narrowed more than 75% in cross-sectional area by atherosclerotic plaque		
LAD	4 (4)	44 arteries (42 > 75%)
LCx	20 (19)	
RCA	20 (19)	
Number of 5 mm segments in 44 nonbypassed coronary arteries and (number of arteries) [%] narrowed more than 75% in cross-sectional area by atherosclerotic plaque	616 (292) [47%]	
Bypassed coronary arteries		
LAD only	9	12 patients (single artery)
LCx only	1	
RCA only	2	
LAD and LCx	10	20 patients (two arteries)
LAD and RCA	9	
LCx and RCA	1	
Bypassed coronary artery and number of arteries narrowed more than 75% in cross-sectional area by atherosclerotic plaque		
LAD	28 (28)	52 arteries (52 > 75%)
LCx	12 (12)	
RCA	12 (12)	
Total number of 5 mm segments in 52 bypassed coronary arteries and (number of arteries) [%] narrowed more than 75% in cross-sectional area by atherosclerotic plaque	728 (375) [52%]	

TABLE II

Angiographic and Histologic Comparison of Amount of Coronary Arterial Narrowing by Atherosclerotic Plaque in 32 of 44 Nonbypassed Major Epicardial Coronary Arteries With Less Than 50 percent Diameter Reduction on Preoperative Angiography

Histologic Finding at Necropsy	Preoperative Angiographic Narrowing (diameter reduction)		
	0–30%	31–50%	Total
LAD			
Number of arteries	1	2	3
Number narrowed >75%*	1	2	3
Number of 5 mm segments	14	29	43
Number (%) narrowed >75%*	6 (43)	13 (45)	19(44)
LCx			
Number of arteries	1	14	15
Number narrowed >75%*	1	14	15
Number of 5 mm segments	5	133	138
Number (%) narrowed >75%*	1 (20)	65 (49)	66 (48)
RCA			
Number of arteries	2	12	14
Number narrowed >75%*	2	11	13
Number of 5 mm segments	46	216	262
Number (%) narrowed >75%*	20 (43)	106 (49)	126 (48)
Totals			
Number of arteries	4	28	32
Number (%) narrowed >75%*	4 (100)	27 (96)	31 (97)
Number of 5 mm segments	65	378	443
Number (%) narrowed >75%*	27 (42)	184 (49)	211 (48)

* Cross-sectional area.

placed to the left obtuse marginal coronary artery, the left circumflex system then was considered to have been bypassed. If neither the left obtuse marginal nor the left circumflex coronary artery had been bypassed, only the status of the left circumflex artery was included in our analysis. Of the 44 nonbypassed coronary arteries, preoperative coronary angiograms showed some degree of narrowing in 43: diameter reduction 10 to 30 percent in 3 arteries, 31 to 50 percent in 28 arteries, 51 to 75 percent in 1 artery and 76 to 100 percent in 11 arteries (Table II). In the latter 12 arteries, either coronary bypass grafting had not been planned (six cases) or at operation the artery was not found or was deemed too small to bypass (six cases). In all 52 bypassed coronary arteries, preoperative selective angiograms disclosed greater than 50 percent narrowing in diameter.

The nonbypassed and bypassed coronary arteries were examined at necropsy in similar fashion. Each artery was excised intact from the heart and subjected to X-ray examination. If calcific deposits were present radiographically the artery was decalcified. The arteries were then cut transversely to the longitudinal axes into 5 mm long segments. The 5 mm segments were labeled, dehydrated and embedded in paraffin; several histologic sections were cut and one was stained by the Movat method and examined. All determinations of luminal narrowing were based on examination of the Movat-stained sections because this stain clearly outlines the artery's internal elastic membrane. The degree of narrowing was based on histologic examination of each cross section magnified 25 to 50 times. The judgment regarding the degree of luminal narrowing of each 5 mm segment was based on the degree of luminal obliteration within the luminal circle bordered by the internal elastic membrane. This method has been demonstrated[1] to be almost as accurate as videoplanimetry and the intra- and interobserver errors to be less than 5 percent. The percent cross-sectional area luminal narrowing by atherosclerotic plaque in each 5 mm segment was determined as follows: 0 to 25, 26 to 50, 51 to 75, 76 to 95 and 96 to 100. In arteries with eccentric lumens and walls indented artifactually into them, the judgment of degrees of narrowing at necropsy was determined only after visual expansion of the collapsed portion of wall.

Results

Nonbypassed versus bypassed coronary arteries: At necropsy, the lumens in 42 (95 percent) of the 44 nonbypassed coronary arteries and the lumens in all 52 bypassed coronary arteries were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaques (Table I). (A 75 percent narrowing of cross-sectional area [necropsy] is equivalent to a 50 percent reduction in diameter [angiogram].[2]) The results of the examination of each 5 mm long segment of the 44 nonbypassed and the 52 bypassed coronary arteries are summarized in Table III and in Figure 1. Of the 616 five mm segments in the 44 nonbypassed arteries, 292 (47 percent) were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque; 143 (23 percent) were narrowed, 51 to 75 percent; 109 (18 percent) were narrowed 26 to 50 percent; and 72 (12 percent) were narrowed 0 to 25 percent. Of the 728 five mm segments in the 52 bypassed arteries 375 (52 percent) were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaques; 215 (29 percent) were narrowed 51 to 75 percent; 123 (17 percent) were narrowed 26 to 50 percent, and 15 (2 percent) were narrowed 0 to 25 percent. The amount of severe (more than 75 percent cross-sectional area) narrowing by atherosclerotic plaques in the proximal and distal halves of the nonbypassed and bypassed left anterior descending and right coronary arteries was similar (Fig. 2). The proximal half of the nonbypassed left circumflex coronary artery had a higher proportion of 5 mm segments narrowed 76 to 100 percent than did the distal half of this

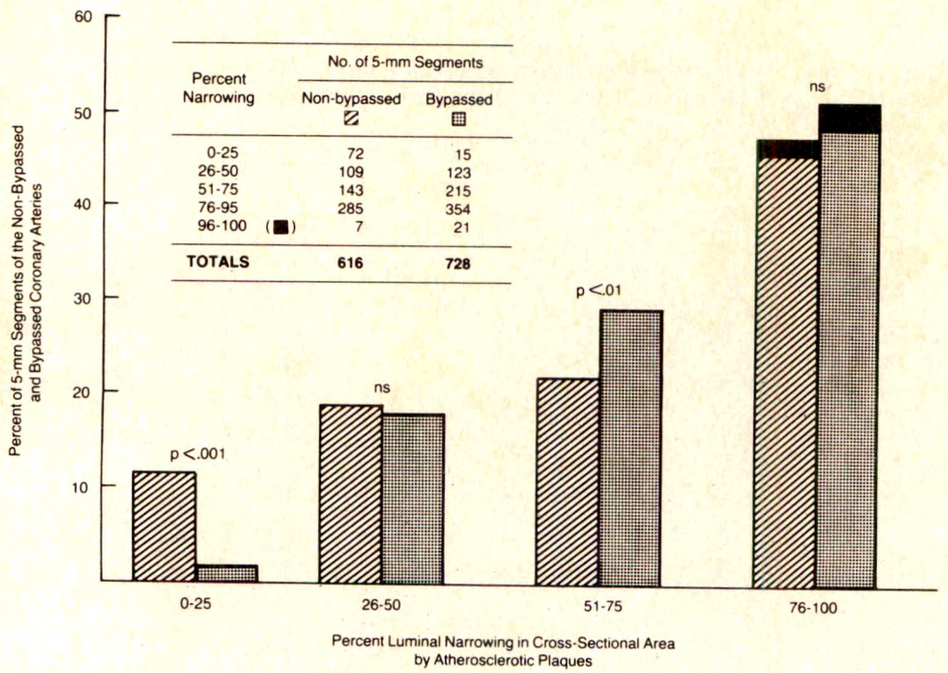


FIGURE 1. Bar graph showing percent of 5 mm segments of 44 nonbypassed and 52 bypassed major epicardial coronary arteries narrowed to various degrees in 32 necropsy patients with angina pectoris who died within 30 days of an aortocoronary bypass operation.

TABLE III

Number and Percent of 5 mm Segments of 44 Nonbypassed (N) and 52 Bypassed (B) Major Epicardial Coronary Arteries and Grade of Cross-Sectional Area Luminal Narrowing

Coronary Artery	Percent Cross-Sectional Area Luminal Narrowing											
	0–25		26–50		51–75		76–95		96–100		Total	
	N	B	N	B	N	B	N	B	N	B	N	B
LAD												
n	6	12	6	72	16	117	25	195	2	8	55	404
%	(11)	(3)	(11)	(18)	(29)	(29)	(45)	(48)	(4)	(2)	(100)	(100)
LCx												
n	28	2	34	28	41	40	95	63	2	4	200	137
%	(14)	(2)	(17)	(20)	(21)	(29)	(47)	(46)	(1)	(3)	(100)	(100)
RCA												
n	38	1	69	23	86	58	165	96	3	9	361	187
%	(11)	(1)	(18)	(12)	(24)	(31)	(46)	(51)	(2)	(5)	(100)	(100)
Total	72	15	109	123	143	215	285	354	7	21	616	728
	(12)†	(2)†	(18)	(17)	(23)*	(29)*	(46)	(49)	(1)	(3)	(100)	(100)

* $p < 0.01$. † $p < 0.001$.
LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery.

artery but the proportions were similar in the bypassed artery.

Preoperative coronary angiographic versus autopsy findings: Of the 32 nonbypassed coronary arteries (in 23 patients) judged to have a diameter reduction of 50 percent or less on preoperative coronary angiography, at necropsy 31 (97 percent) were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque (211 [48 percent] of 443 five mm segments) and 1 (3 percent) was narrowed 51 to 75 percent in cross-sectional area (Table II). Figures 3 and 4 show, respectively, a cross section from each 5 mm segment of the right coronary artery and the angiogram of this artery in 1 of the 23 patients with one or more major coronary arteries that were not bypassed because of insignificant reduction in diameter. Of the 12 nonbypassed coronary arteries (in nine patients) judged to be either "severely narrowed" or "too small to bypass" on preoperative coronary angiography, at necropsy 11 were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque (81 [47 percent] of 173 five mm segments) and 1 was narrowed 51 to 75 percent.

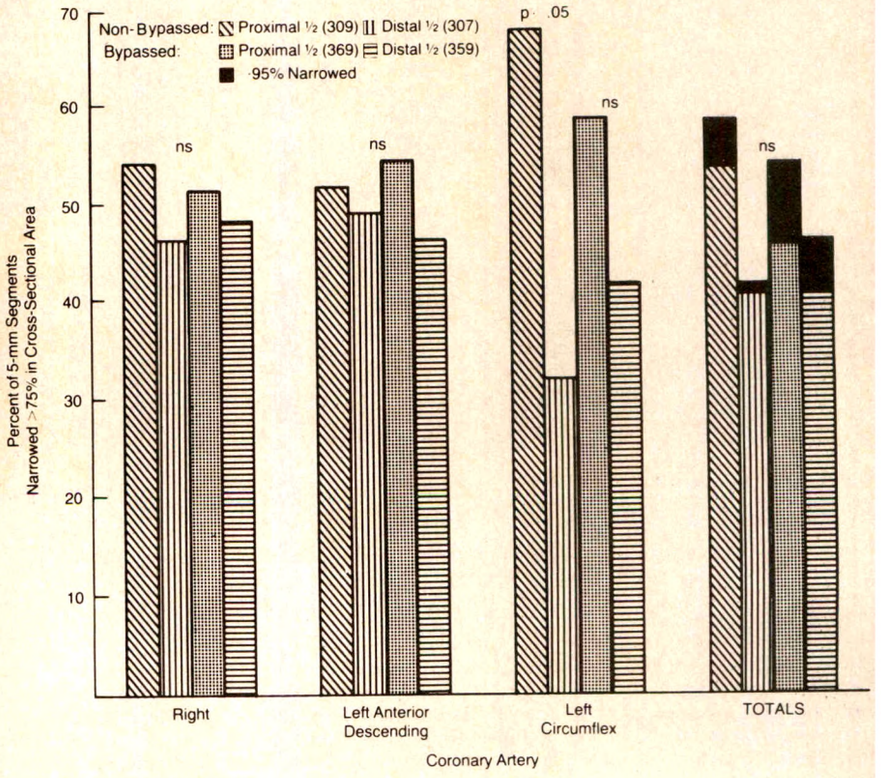


FIGURE 2. Bar graph showing percent of 5 mm segments of the proximal and distal halves of the 44 nonbypassed and 52 bypassed major epicardial coronary arteries narrowed more than 75 percent in cross-sectional area by atherosclerotic plaque in 32 necropsy patients who died within 30 days of aortocoronary bypass grafting.

Comments

Autopsy findings in fatal coronary artery disease: This study demonstrates that our necropsy patients with angina pectoris who died soon after aortocoronary bypass operations had *diffuse* coronary atherosclerosis and that their preoperative angiograms frequently underestimated the severity of the coronary narrowing. Other studies from this laboratory and elsewhere have also shown that among patients with fatal coronary heart disease (irrespective of the type of coronary event), coronary atherosclerosis in the major epicardial coronary arteries is diffuse and severe and that it is unusual to find a normal 5 mm long segment in any of the three major (right, left anterior descending and left

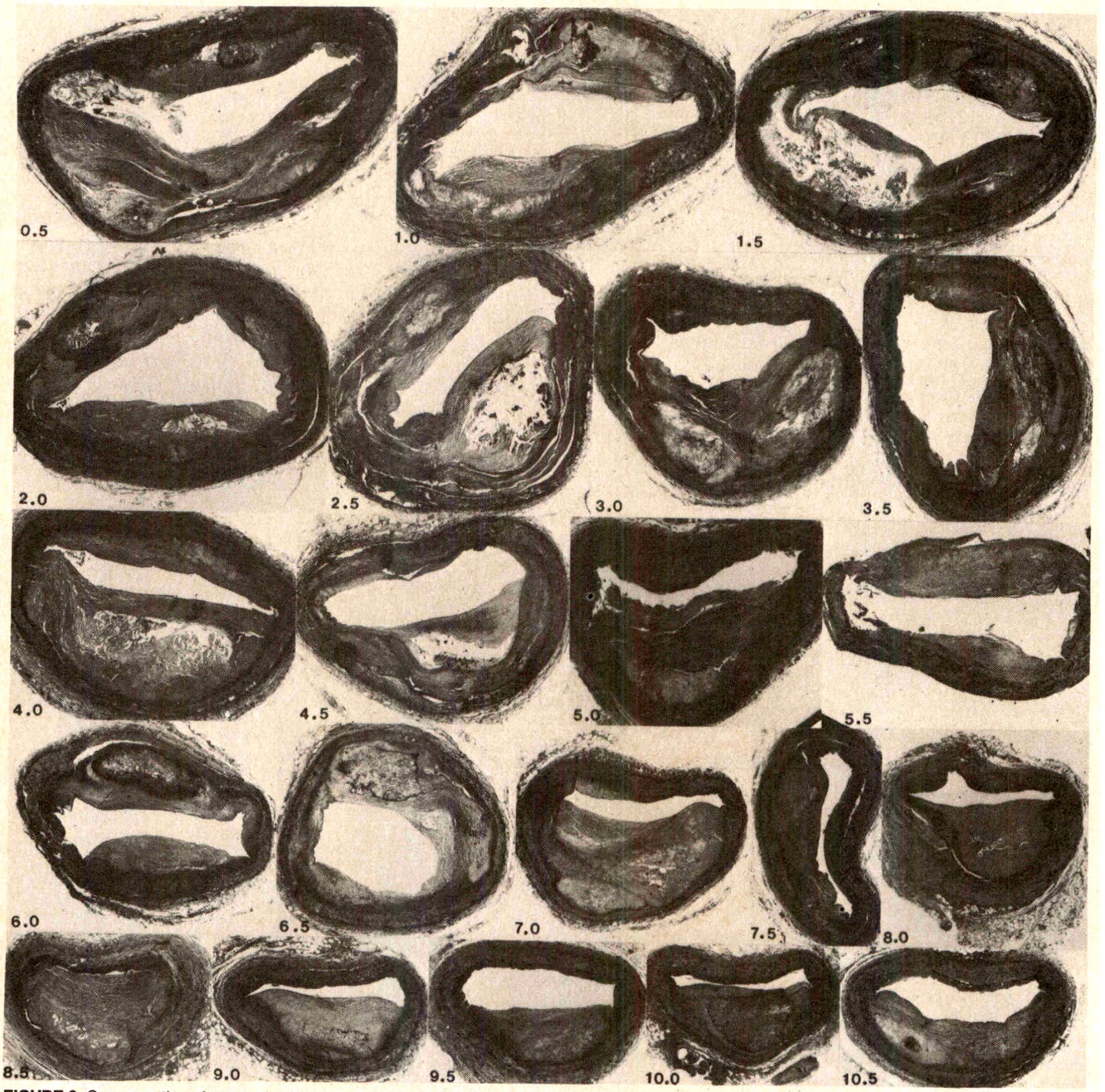


FIGURE 3. Cross-sections from each of 21 five mm segments of the right coronary artery in 1 of the 32 patients in whom one or more major coronary arteries were not bypassed because the preoperative angiogram indicated 50 percent or less diameter reduction. The histologic sections begin with the first 5 mm segment of the right coronary artery (0.5 cm) and extend to the origin of the posterior descending branch (10.5 cm). The amount narrowing of cross-sectional area of the lumen by atherosclerotic plaque (determined with videoplanimetry) in these 21 histologic sections was as follows: 76 to 100 percent in 10 (48 percent), 51 to 75 percent in 6 (28 percent) and 50 percent or less in 5 (24 percent).

circumflex) coronary arteries.[3-8] Among necropsy patients studied in our laboratory with unstable angina pectoris,[4] acute myocardial infarction,[5] sudden coronary death[6] and healed myocardial infarction with either cardiac[7] or noncardiac[8] death, the lumens of at least 30 percent of the three major coronary arteries were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque and about 70 percent of the lengths of these three arteries were narrowed more than 50 percent in cross-sectional area. Additionally, the lumens in only about 10 percent of the lengths of these three arteries were narrowed 25 percent or less in cross-sectional area. Among the 44 nonbypassed coronary arteries in our 32 patients, 292 (47 percent) of 616 five mm segments (an average of 20/artery) of nonbypassed artery were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque and another 23 percent were narrowed 51 to 75 percent. Of the 52 bypassed coronary arteries in our 32 patients, 375 (52 percent) of 728 five mm segments were narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque and another 29 percent were narrowed 51 to 75 percent. Furthermore, only 12 percent of the 5 mm long segments of the nonbypassed coronary arteries were narrowed 25 percent or less, and only 2 percent of the bypassed arteries were so narrowed. Thus, the odds appear to favor the view that all three major coronary arteries will be considerably narrowed in necropsy patients with angina pectoris who died early after an aortocoronary bypass operation.

Coronary angiographic versus autopsy findings: Several studies among patients with symptomatic coronary heart disease have emphasized that coronary angiograms tend to underestimate the amount of coronary luminal narrowing. Among 61 coronary arteries examined with angiography during life and subsequently at necropsy in our laboratory,[2] in 17 (40 percent) of the 42 vessels narrowed 76 to 100 percent in cross-sectional area at necropsy, the narrowing was underestimated by two or three angiographers; and in 7 of 8 arteries narrowed 51 to 75 percent in cross-sectional area at necropsy, the narrowing was underestimated by one or more of the three angiographers. Thus, among patients with severe coronary atherosclerosis, coronary angiography tends to underestimate the actual degrees of luminal narrowing. Among 32 (76 percent) of the 44 nonbypassed coronary arteries (from 23 patients) described in this study, preoperative coronary angiography indicated less than 50 percent reduction in diameter in 21 arteries and 50 percent reduction in 11. However, at necropsy 31 of these 32 arteries were narrowed more than 75 percent in cross-sectional area.

Role of coronary bypass grafting: Several clinical studies have demonstrated that the early postoperative mortality rates and the frequency of postoperative acute

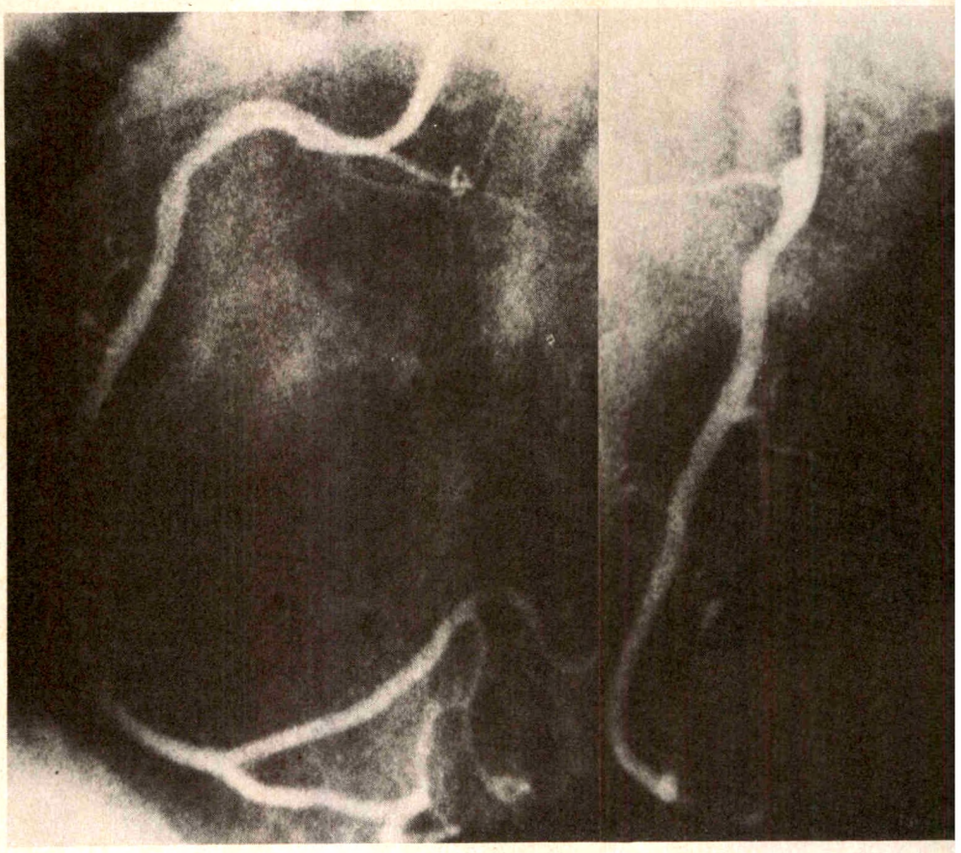


FIGURE 4. Same patient. Two views of the preoperative selective coronary arteriogram of the right coronary artery in the patient whose right coronary artery is shown histologically in Figure 3. The maximal diameter reduction in both right (**right**) and left (**left**) anterior oblique views was judged to be between 40 and 50 percent.

myocardial infarction are lower, and the frequency of disappearance of angina pectoris and improvement in exercise tolerance are greater in patients having three or more aortocoronary grafts than in those with two grafts and less in patients having two grafts than in those having only one. Stiles et al.[9] found the combined immediate and 6 month mortality rate to be 4 percent in 445 patients receiving three grafts, 9 percent in the 416 patients receiving two grafts and 21 percent in the 85 patients receiving a single graft. Sheldon et al.[10] observed clinical evidence of acute myocardial infarction early postoperatively in only 6 (3 percent) of 187 patients having multiple grafts and in 49 (17 percent) of 286 patients having a single graft. Of 58 patients followed up 13 to 36 months by Assad-Morell et al.,[11] 21 (80 percent) of 26 receiving three or more grafts had no angina pectoris compared with 12 (63 percent) of 19 patients receiving two grafts and only two (16 percent) of 13 patients with a single graft. Sheldon et al.[10] reported similar results. Consequently, the frequency of a second coronary bypass operation for recurrence of angina pectoris also is much greater in patients having one or two grafts inserted in the first aortocoronary bypass procedure compared with those having three or more grafts inserted in the first operation.[12–17] Assad-Morell et al.[11] found "positive" ischemic exercise responses with the exercise (stress) treadmill test in only 2 (9 percent) of 23 patients with three or more grafts, in 23 (70 percent) of 30 patients with two grafts and in 23 (96 percent) of 24 patients with only one graft.

Finally, progression of the atherosclerotic process in nonbypassed coronary arteries appears to be the major cause of recurrence of myocardial ischemia late after aortocoronary bypass operation. Seides et al.[18] restudied 22 patients 53 to 84 months after aortocoronary bypass grafting who had had at least one graft patent 3 to 9 months after the bypass operation. At the late study, 31 of 33 grafts were patent, but angina pectoris had reappeared in 11 of 16 patients who had become asymptomatic early after operation. Progression of narrowing in ungrafted coronary arteries accounted for the clinical deterioration in 9 of these 11 patients.

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Results of Operation for Obstructive Hypertrophic Cardiomyopathy In the Elderly

Septal Myotomy and Myectomy in 20 Patients 65 Years of Age or Older

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The results of operative treatment in 20 patients with hypertrophic cardiomyopathy 65 years of age or older are described. All 20 patients were severely symptomatic before operation. Seventeen of the 20 patients had marked left ventricular outflow tract obstruction under basal conditions (average pressure gradient 107 mm Hg); the other three patients had outflow gradients of more than 50 mm Hg only with provocation. One patient died at operation, and one died 4 years after operation of circumstances unrelated to hypertrophic cardiomyopathy. Sixteen of the 18 long-term survivors have had persistent and significant functional improvement for up to 6 years after operation, including 7 patients who are now asymptomatic. Two patients experienced symptomatic deterioration after manifesting initial symptomatic improvement for 3 and 4 years, respectively, after operation. Operation resulted in a marked decrease or abolition of the left ventricular outflow gradient in each of the 17 patients studied with postoperative cardiac catheterization.

These data show that gratifying symptomatic and hemodynamic improvement may be obtained by septal myotomy and myectomy in the elderly patient with hypertrophic cardiomyopathy. Accordingly, advanced age in itself is not a contraindication to operative intervention in such patients.

Hypertrophic cardiomyopathy is usually considered a disease of the young and the middle-aged, because most patients become symptomatic or experience sudden death before 65 years of age.[1–4] However, with the advent of echocardiography in the early 1970s[5–7] hypertrophic cardiomyopathy has been identified with increasing frequency in older patients.[8–17] The recognition that hypertrophic cardiomyopathy commonly produces marked functional limitation in older patients requires that the role of operation in the management of such patients be defined. For these reasons the present study was undertaken. Our report describes the clinical features and results of operation in 20 patients 65 years of age or older with hypertrophic cardiomyopathy who underwent septal myotomy and myectomy at the National Heart, Lung, and Blood Institute.

Selection of Patients

Between January 1960 and May 1980, a total of 276 patients with hypertrophic cardiomyopathy were operated on at the National Heart, Lung, and Blood Institute. Among them were 21 patients who were 65 years of age or older at the time of septal myotomy and myectomy. All were operated on after 1972. Twenty of the 21 patients were followed up for at least 1 year and constitute the present study group. The 20 patients ranged in age from 65 to 76 years (mean 69); 17 were women and only 3 were men.

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Indications for operation were the same as those for other patients with hypertrophic cardiomyopathy at our institution[4,18]: (1) severe symptoms (New York Association[19] functional class III or IV) unresponsive to treatment with propranolol and, for the past year, with verapamil; (2) marked left ventricular outflow tract obstruction (50 mm Hg or greater subaortic gradient under basal conditions or with provocative maneuvers; and (3) absence of a severe medical condition constituting a contraindication to a cardiac operation. At the time of operation, 9 patients were in functional class IV and the other 11 patients were in functional class III. The most common symptoms experienced were fatigue, dyspnea on exertion and chest pain (Table I). The patients had been symptomatic for 1 to 26 years (mean 9) before operation, and hypertrophic cardiomyopathy was initially identified 1 to 14 years (mean 4) before operation. Nineteen of the 20 patients had diseases in addition to hypertrophic cardiomyopathy, including 5 patients in whom more than one organ system was involved (Table II).

Results

Preoperative Clinical Findings

Hemodynamic data: Right and left heart catheterization was performed preoperatively in each of the 20 patients. The peak systolic pressure gradient between the left ventricle and a systemic artery under basal conditions was greater than 50 mm Hg in 17 of the 20 patients studied (range 55 to 170 mm Hg; average 103). The three patients who had an outflow gradient of less than 50 mm Hg under basal conditions had a gradient of 80 to 130 mm Hg with provocative maneuvers (Valsalva maneuver, amyl nitrite inhalation or isoproterenol infusion). Left ventricular end-diastolic pressure ranged from 7 to 36 mm Hg (average 18) and was abnormal (greater than 12 mm Hg) in 13 of the 20 patients.

Fifteen of the 20 study patients had preoperative coronary arteriograms, which revealed significant coronary artery disease (greater than 50 percent luminal narrowing of at least one major extramural artery) in 2 patients, and mild or no abnormalities in the other 13. None of the lesions identified was considered severe enough to warrant aortocoronary bypass surgery. One other patient had associated mild aortic valve stenosis (peak systolic gradient 30 mm Hg).

TABLE I

Preoperative Symptoms in 20 Patients 65 Years of Age and Over Who Underwent Operation for Obstructive Hypertrophic Cardiomyopathy

Symptoms	Patients n (%)
Fatigue	20 (100)
Dyspnea on exertion	19 (95)
Chest pain*	15 (75)
Syncope	11 (55)
Orthopnea	11 (55)
Paroxysmal nocturnal dyspnea	6 (30)
Presyncope	6 (30)
Palpitations	5 (25)

* Thirteen of these 15 patients had typical angina pectoris; the remaining 2 patients had atypical chest pain.

Echocardiographic findings: Echocardiograms were performed preoperatively in 18 of the 20 patients. Ventricular septal thickness (measured just below the caudal margins of the mitral leaflets) ranged from 16 to 32 mm (mean 24) and was greater than 20 mm in 13 patients. Asymmetric septal hypertrophy (ventricular septal to posterior free wall thickness ratio 1.3 or greater) was present in each of the 18 patients; septal/free wall ratios ranged from 1.3 to 2.7 (mean 1.9). Systolic anterior motion of the anterior mitral leaflet was present under basal conditions in 14 of the 18 patients, and absent in 2 others; in the remaining 2 patients, the mitral valve was not adequately imaged to assess systolic anterior motion. In every patient studied, the left atrial transverse dimension was increased relative to body surface area (range 40 to 59 mm; mean 49). Mitral anular calcification was identified in 6 patients; this finding was confirmed in each of these patients with fluoroscopy.

Electrocardiographic data: Five of the 20 patients had a normal electrocardiogram, and 2 others had only S-T segment and T wave changes. In the remaining patients the most common findings were left ventricular hypertrophy (five patients), S-T segment and T wave changes (six patients) and left atrial enlargement (four patients). Six patients had conduction abnormalities, including first degree heart block (one patient), Wolff-Parkinson-White pattern (one patient), right bundle branch block (one patient) and intraventricular conduction defect (two patients). One patient had complete heart block before operation and required permanent implantation of a pacemaker. Five other patients had had paroxysmal atrial fibrillation preoperatively, but no patient had atrial fibrillation at the time of operation.

Short-Term Postoperative Follow-Up

After septal myotomy and myectomy,[18] the period of hospitalization ranged from 10 to 32 days (mean 16).

TABLE II

Associated Cardiovascular and Medical Diseases in 20 Patients, 65 Years of Age or Older, Who Underwent Operation for Obstructive Hypertrophic Cardiomyopathy

Disease	Patients n (%)
Systemic hypertension	12 (60)
Peptic ulcer disease	3 (15)
Coronary artery disease	2 (10)
Diabetes mellitus*	2 (10)
Chronic obstructive pulmonary disease	2 (10)
Acquired valvular heart disease†	1 (5)
Renal disease‡	1 (5)
Hypothyroidism	1 (5)

* Diabetes of adult onset controlled with diet alone. † Mild aortic valve stenosis with a 30 mm Hg peak systolic pressure gradient; at the time of myotomy and myectomy, the valve was found to be symmetrical and tricuspid. There was no fusion of any commissure, and there was minimal calcification at the base of each sinus. Valve replacement was not necessary. ‡ Interstitial nephritis believed to be a result of analgesic medication abuse.

The postoperative period was free of serious complications in 17 of the 20 patients. One patient died on the 2nd postoperative day, after sustaining a myocardial infarction during exploration for postoperative bleeding secondary to a right ventricular laceration. In two other patients complete heart block developed after operation, and implantation of a permanent pacemaker was required.

Long-Term Postoperative Follow-Up

Clinical state: The postoperative follow-up period ranges from 1 to 6 years (mean 4). Of the 19 patients who survived operation, 18 are currently alive (Fig. 1). Their ages now range from 68 to 81 years (mean 72). Sixteen of these 18 patients have experienced significant functional improvement by at least one functional class compared with their preoperative state, including 7 who are currently asymptomatic (Fig. 2). The remaining two patients reported marked alleviation of their symptoms for 3 and 4 years, respectively, after operation, but subsequently returned to their preoperative functional status. One of these two patients had mitral stenosis (10 mm Hg mean gradient) identified for the first time 3 years after operation (at age 79). One other patient died 4 years after operation (at age 81) after experiencing a severe infarction during an inferior vena caval plication for recurrent pulmonary emboli.

Hemodynamic findings: Seventeen of the 19 operative survivors underwent cardiac catheterization 6 to 12 months after operation. In each of the 17 patients, the left ventricular outflow tract gradient under basal conditions was either abolished or significantly reduced by operation (Fig. 3). No outflow gradient was present under basal conditions in nine patients; the gradient was 10 mm Hg or less in six patients and 20 and 30 mm Hg, respectively, in two other patients. In 14 of the 17 patients, an outflow gradient of 12 to 130 mm Hg (average 62) was elicited with provocative maneuvers postoperatively. Of the 13 patients with an abnormal preoperative left ventricular end-diastolic pressure, the postoperative end-diastolic pressure was decreased in 10 patients (including 5 in whom it became normal) and increased in 3 other patients.

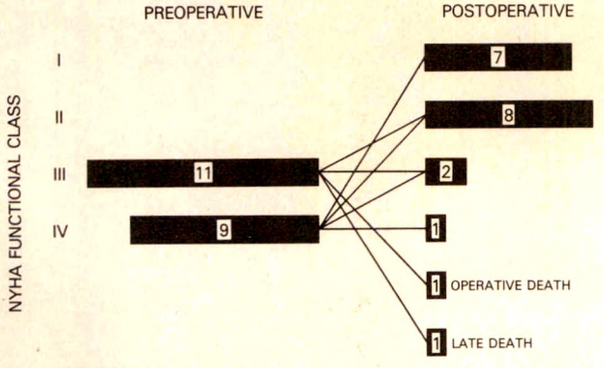


FIGURE 2. New York Heart Association (NYHA) functional status and clinical outcome in 20 patients 65 years of age or older (latest follow-up).

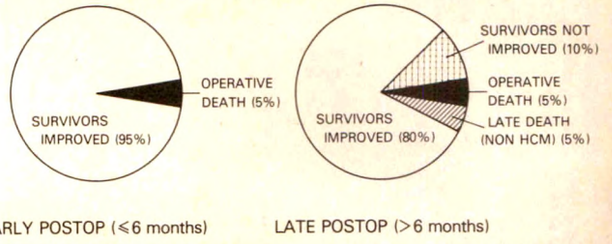


FIGURE 1. Early and late postoperative (POSTOP) course in 20 patients, 65 years of age or older with obstructive hypertrophic cardiomyopathy (HCM).

Echocardiographic findings: Echocardiograms were obtained in 12 patients, 6 months to 4 years after operation. Ventricular septal thickness ranged from 12 mm to 26 mm (mean 17) and was less than the preoperative value (by 2 to 17 mm, mean 7) in each patient. Posterior left ventricular free wall thickness ranged from 8 to 17 mm, and remained unchanged compared with the preoperative value in 11 of the 12 patients; it decreased by 4 mm in the other patient. In 10 of the 12 patients, systolic anterior motion of the anterior mitral leaflet was either absent or mild; in 9 of these 10 patients this motion was clearly reduced in magnitude compared with that in the preoperative tracing; in the remaining 2 patients the mitral valve could not be adequately visualized. In the 10 patients whose left atrial

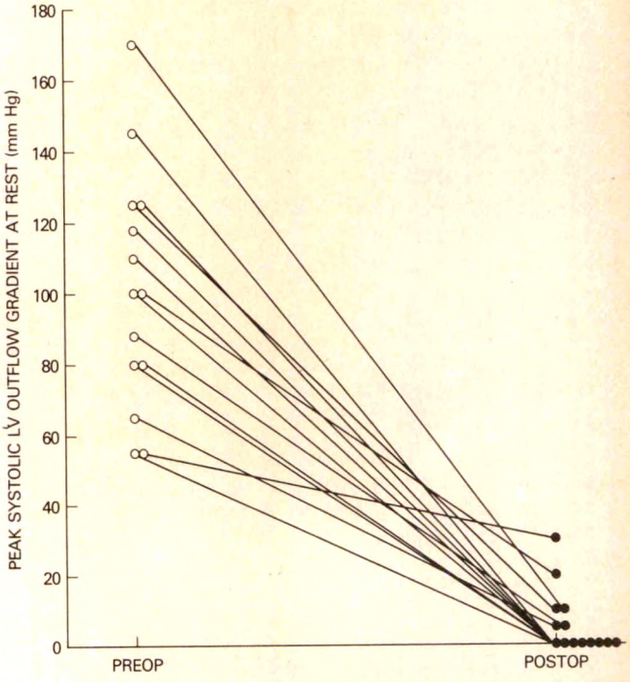


FIGURE 3. Peak systolic pressure gradient between the left ventricle (LV) and systemic artery, measured preoperatively (PREOP) and postoperatively (POSTOP) under basal conditions in 14 patients, 65 years of age and older, who had a preoperative outflow gradient of more than 50 mm Hg.

transverse dimension could be evaluated both before and after operation, it was unchanged from the preoperative value in 4 patients, was increased in 1 and decreased in 5 others.

Discussion

Our findings show that septal myotomy and myectomy can be successfully and safely performed in patients of advanced age (65 years or more) who have hypertrophic cardiomyopathy. Morbidity and mortality associated with operation were not greater in these patients than in patients operated on earlier in life at our institution.[4,18,20] Therefore, septal myotomy and myectomy should be considered in patients of this age group who do not obtain adequate symptomatic benefit from either propranolol or verapamil.[21]

Comparison with results in younger patients: The favorable postoperative symptomatic relief and hemodynamic changes in our elderly patients were also similar to those observed after operation in younger patients with hypertrophic cardiomyopathy.[4,16] For example, almost 90 percent of the elderly operative survivors enjoyed substantial and persistent functional improvement for up to 6 years after operation. Such improvement was particularly gratifying for two reasons: (1) at the time of operation the patient group showed particularly marked functional limitation (almost half were in functional class IV); and (2) all but 1 of the 20 patients had, in addition to hypertrophic cardiomyopathy, another clinically significant cardiovascular or medical abnormality. In many patients, these associated diseases could have adversely affected their operative and postoperative prognosis. Indeed, the patient who died late after operation and the two patients who did not derive long-lasting symptomatic benefit from operation had substantial associated medical problems.

Role of sex and hypertension: Our subgroup of elderly patients differs clinically in two respects from the younger patients who underwent operation for obstructive hypertrophic cardiomyopathy at our institution.[4,15,16] First, the present study group showed a striking predominance of women (85 percent compared with 47 percent for the other 255 patients operated on at this institute since 1960 [$p < 0.001$][15,16]). It is likely that this sex distribution is partly related to patient selection. A greater proportion of men with hypertrophic cardiomyopathy had already died before the age of 65 years and were therefore not found as frequently in a population of elderly patients with this disease. Second, 60 percent of the patients in this study had systemic hypertension preoperatively, a prevalence far exceeding that observed in the younger patient group. This frequent association of hypertension and hypertrophic cardiomyopathy[8,9,11,14] probably reflects only the expected high prevalence rate of systemic hypertension in patients of advanced age and is not causually related to hypertrophic cardiomyopathy.

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

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Indications: Prevention and treatment of angina pectoris attacks.

Contraindications: May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Should not be employed in patients with known idiosyncrasies to nitrites.

Warning: In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Precautions: A hypotensive headache is a sign of overdosage. Occasionally elderly patients may have no untoward symptoms while recumbent but may develop postural hypotension with faintness upon suddenly arising.

Dosage and Administration: For angina pectoris the ointment may be applied every 3 to 4 hours as required. The usual dose is 1 to 2 inches, as squeezed from the tube, although some patients may require as much as 4 or 5 inches. The ointment should be spread in a thin uniform layer on the skin. The optimum dosage is determined by starting with an application of ½ inch of ointment and increasing the dose in ½ inch increments each successive application until headache occurs, then decreasing to the largest dose which does not cause headache. Nitrol Ointment can be applied to any convenient skin area but psychologically, many patients prefer the chest.

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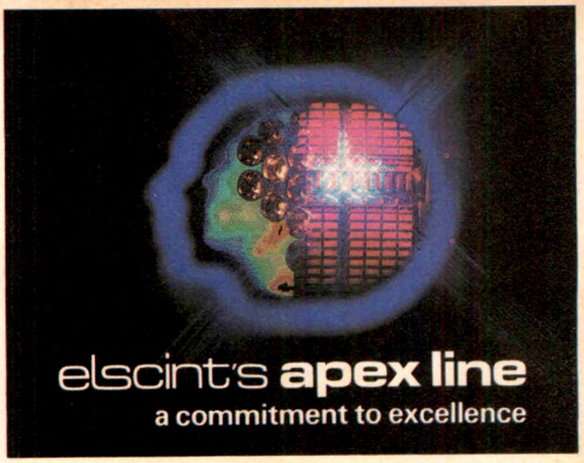

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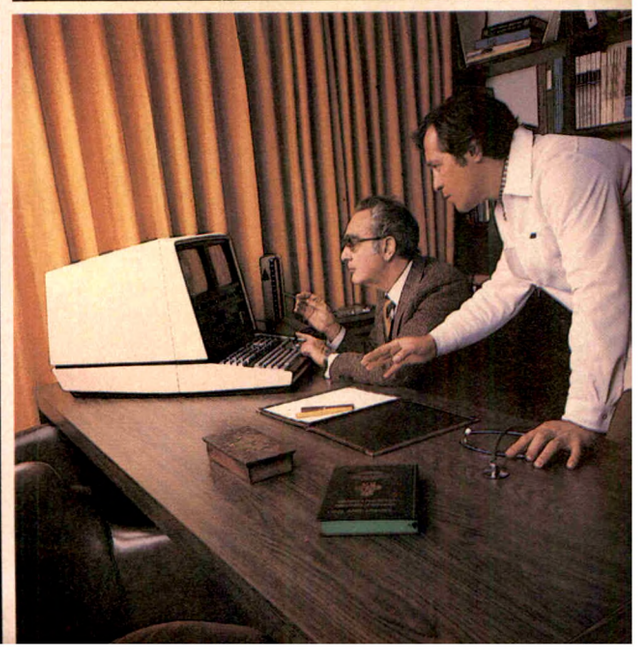
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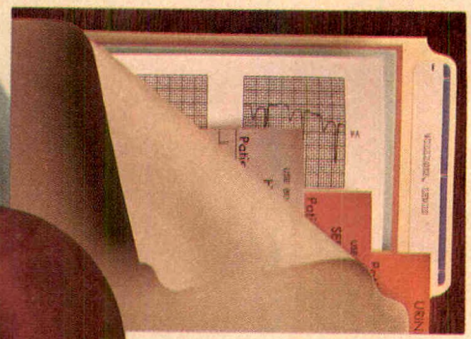


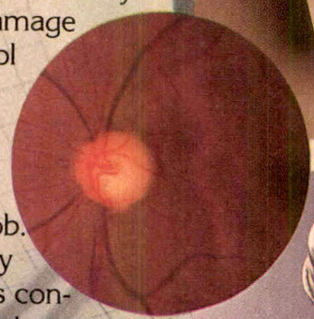
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The patient is 30 pounds overweight, smokes several cigars a day, and has a sedentary office job. He admits he likes his food highly spiced—and over-salted. Besides considering appropriate antihypertensive agents, you may also wish to design a treatment program that includes weight control, salt restriction and exercise.







ROCHE

ANXIETY
MAY WELL BE YOUR DIAGNOSIS
OF HIS PSYCHOLOGICAL CONDITION

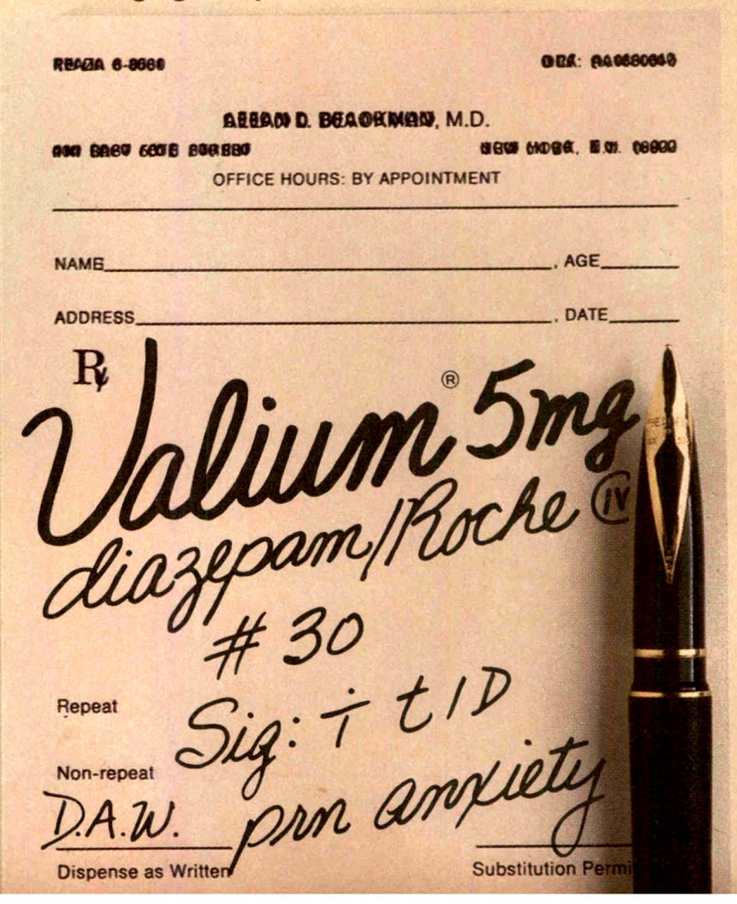


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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available in trays of 10.

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Aldactone®
(spironolactone)

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Warnings). Aldactone should be used only in those conditions described under Indications. Unnecessary use of this drug should be avoided.

Indications: *Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.*
Contraindications: *Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.*
Warnings: *Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.*
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.
Precautions: *Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.*
Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.
Adverse Reactions: *Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.*
Dosage and Administration
For primary hyperaldosteronism: *400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.*
For edema in adults: *Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.*
For edema in children: *Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.*
For essential hypertension: *Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.*
For hypokalemia: *25 to 100 mg. daily in divided doses.*

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When other measures are considered
inadequate or inappropriate

Aldactone®
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The uncomplicator in CHF therapy

- ☑ *Aldactone, an effective diuretic in its own right, also enhances the efficacy of other diuretic agents.*
- ☑ *The unique potassium-regulating mechanism of Aldactone can prevent hypokalemia with limited risk of hyperkalemia. This helps protect your patient from digitalis-induced arrhythmias.*
- ☑ *Unlike other potassium-sparers, Aldactone specifically antagonizes aldosterone, thereby mitigating secondary volume buildup.*

For these reasons, Aldactone is a valuable adjunct in the treatment of CHF.

"Round-the-house" edema, electrolyte washout, subtle secondary volume buildup



***Limitations to Consider**: Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and* Warnings *section of Aldactone prescribing information.)*

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the preceding page.

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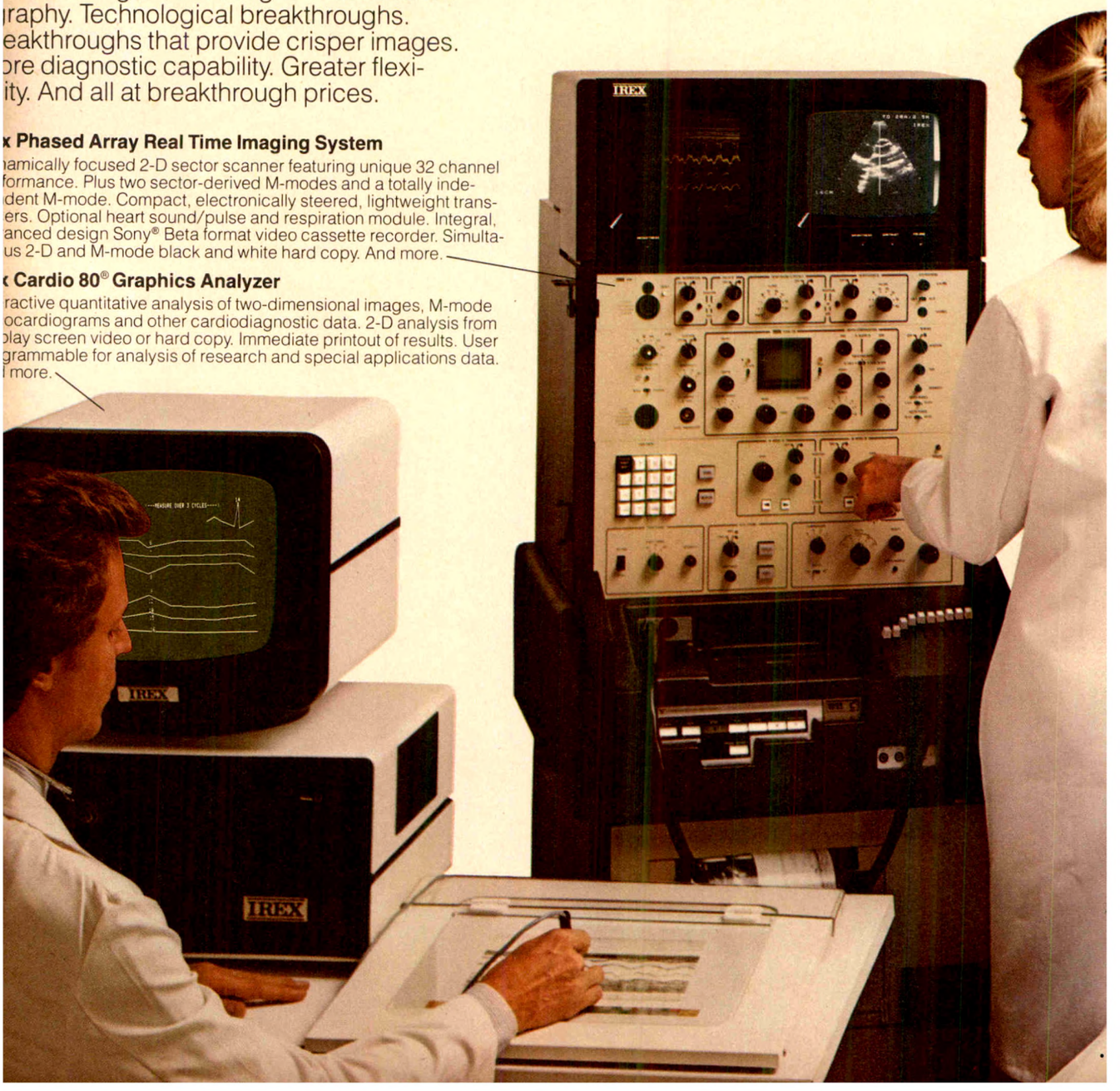
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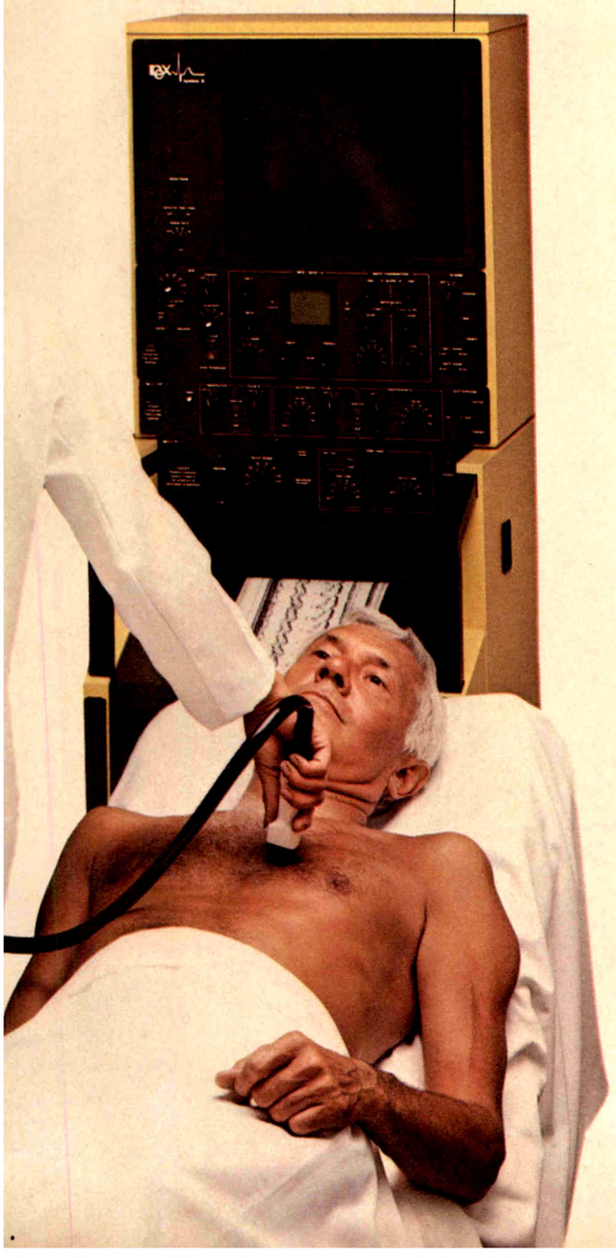
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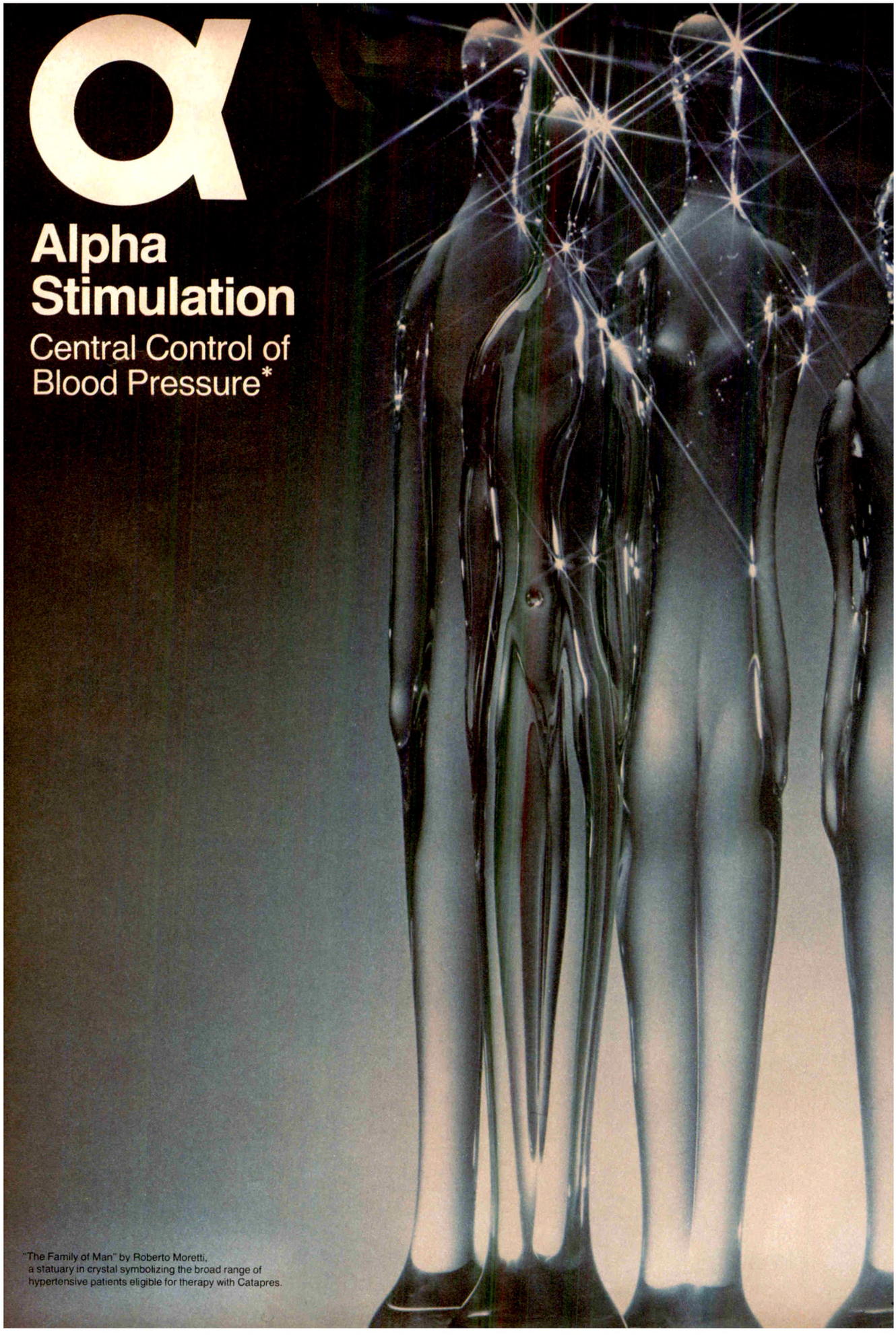
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Like any antihypertensive, use with caution in severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

work/play—normal hemodynamic responses to exercise maintained.

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cardiac output—tends to return to control values during long-term therapy.

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Other factors must include:

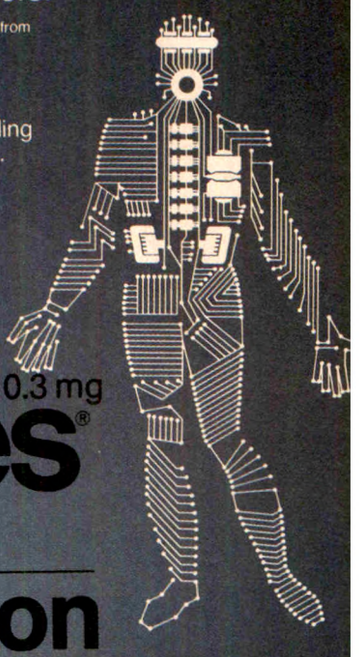
The drug's effectiveness in a given patient, its side effects, warnings, precautions, tolerance, etc. A rational therapeutic choice depends on a careful assessment of all such factors.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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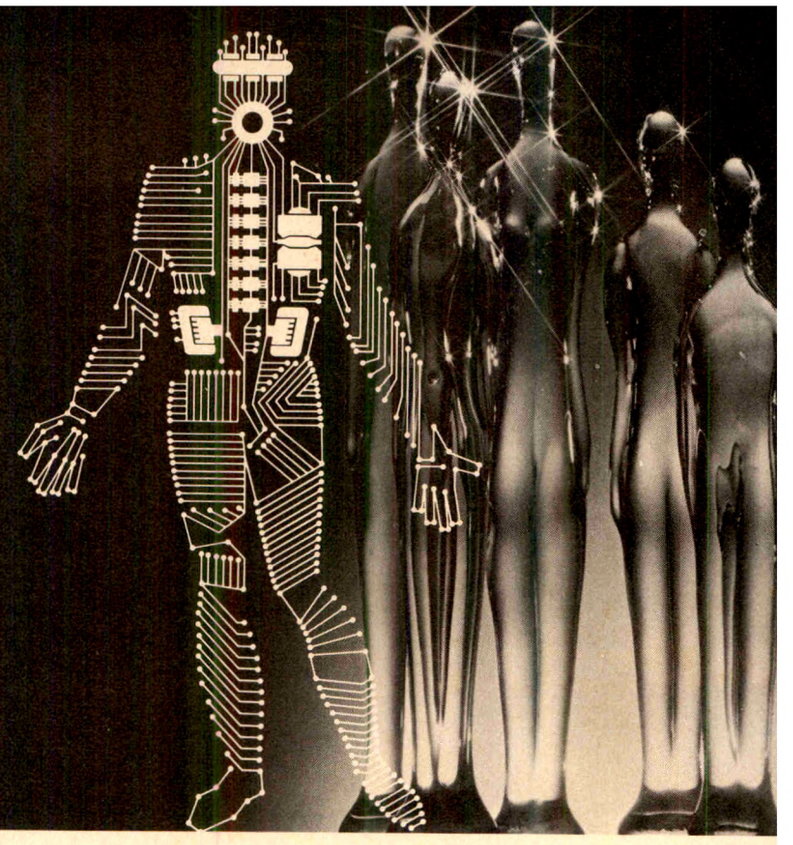


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Hypertension

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Hypertension

- No contraindications.
- Effective in all degrees of hypertension. It is mild to moderate in potency.
- Low incidence of depression, impotence, orthostatic hypotension—no fatal hepatotoxicity.
- Preserves kidney blood flow.

Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at bre fast and 0.1 mg at bedtime. Some patients may ben from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
(clonidine hydrochloride)
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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mo longer.

Adverse Reactions: The most common reactions are dry mouth, drowsine sedation. Constipation, dizziness, headache, and fatigue have been re Generally these effects tend to diminish with continued therapy. The fo reactions have been associated with the drug, some of them rarely. (Ir instances an exact causal relationship has not been established.) These i Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnorma liver function tests; one report of possible drug-induced hepatitis without and hyperbilirubinemia in a patient receiving clonidine hydrochloride, thalidone and papaverine hydrochloride. Weight gain, transient elevation o glucose, or serum creatine phosphokinase: congestive heart failure, Ray phenomenon; vivid dreams or nightmares, insomnia, other behavioral ch nervousness, restlessness, anxiety and mental depression. Also ras gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not ass with a rash, impotence, urinary retention, increased sensitivity to alcohol, dr itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecor weakly positive Coombs' test, asymptomatic electrocardiographic abnorn manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished sent reflexes and vomiting followed the accidental ingestion of Catapres (cl hydrochloride) by several children from 19 months to 5 years of age. lavage and administration of an analeptic and vasopressor led to compl covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30- intervals usually abolishes all effects of Catapres, (clonidine hydrochloride dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 100 available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.
For complete details, please see full prescribing information.
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Lidocaine-Induced Reduction in Size of Experimental Myocardial Infarction

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with the technical assistance of
JERRY D. DEWEY

Rochester, Minnesota

In anesthetized open chest dogs, the effects of therapeutic doses of lidocaine on myocardial cell respiration, creatine kinase depletion, left ventricular stroke work and cardiac necrosis were assessed. The dogs were subjected to 40 minutes of occlusion of the left anterior descending coronary artery, followed by 5 hours of reperfusion. Group I (12 dogs) had infusion of saline solution; group II (8 dogs) had infusion of 0.2 mg/kg per min of lidocaine (serum level 16.8 ± 1.4 μg/ml); group III (5 dogs) had infusion of 0.04 mg/kg per min of lidocaine (serum level 3.6 μg/ml). Ischemic regional myocardial blood flow (measured by 9 μm spheres of strontium-85) was 6.34 ± 1.62 ml/100 mg per min in group I, 1.48 ± 0.59 in group II ($p < 0.05$) and 1.32 ± 0.50 in group III ($p < 0.05$). Oxygen consumed during conversion of adenosine diphosphate to adenosine triphosphate in mitochondria from control and lidocaine-treated ischemic tissue was depressed ($p < 0.05$) and correlated ($r = 0.63$) with creatine kinase depletion. Left ventricular stroke work was not significantly different among the three groups. Infarct size (in percent of left ventricular weight) was 12.6 ± 2.0 for group I, 4.8 ± 1.2 for group II ($p < 0.01$) and 4.8 ± 2.5 for group III ($p < 0.05$). The data suggest that the reduction of myocardial infarct size by lidocaine was not dependent on enhanced myocardial blood flow and was independent of left ventricular stroke work.

In the clinical setting of acute myocardial ischemia, preservation of viable myocardium is the major aim of any intervention, be it surgical revascularization,[1] medical reduction of myocardial oxygen utilization,[2] stimulation of ischemic anaerobic glycolysis[3] or enhancement of substrate transport.[4,5] Although the bioenergetics, pathophysiology and ultrastructure of myocardial ischemia have been investigated extensively during the past decade, the events that determine irreversible cell injury still remain unknown.

By depriving the myocardium of oxygen, ischemia hinders not only efficient oxidation of substrates and energy production but also normal cellular and subcellular function, thereby particularly disrupting membrane integrity[6] and electrolyte homeostasis.[7] Considerable evidence suggests that the ultrastructural changes after ischemia are due to an increase in permeability of cardiac cell membranes.[6] In addition, cardiac mitochondria undergo morphologic, functional and ultrastructural changes, either simultaneously with or shortly after irreversible damage.[7] An uncoupling of energy production and utilization has been proposed in acute ischemia.[8] In view of depressed mechanical function in the presence of measurable energy-rich phosphates, perhaps a deficiency exists in the transfer of adenosine triphosphate and creatine phosphate from mitochondria to their sites of utilization. After reperfusion of ischemic myocardium, changes in intracellular water and electrolytes are rapid and of significant magnitude; therefore, defects in the cell's ability to regulate water and electrolyte homeostasis may be an important or even a primary event in the pathogenesis of irreversible cell injury.[6] Increased permeability of cellular and subcellular membranes after myocardial ischemia has been demonstrated[9–11] by

From the Division of Cardiovascular Diseases and Internal Medicine, and the Department of Pathology and Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. This investigation was supported in part by Research Grant HL-12997 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland. Manuscript received March 17, 1980; revised manuscript received June 26, 1980, accepted July 7, 1980.

Address for reprints: Carlos E. Harrison, Jr., MD, Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55901.

the use of tracer particles; by the release of intracellular enzymes; by an increased influx of sodium, chlorine, water and calcium; and by an increased efflux of potassium and magnesium.

If alterations in membrane permeability are a major factor in myocardial damage after ischemic episodes, membrane-stabilizing agents may reduce this damage. Propranolol and corticosteroids, both membrane-stabilizing agents, are effective in myocardial ischemic protection.[12] Verapamil,[13] nifedipine[14] and diltiazem[15] are all calcium channel antagonists and protect the ischemic myocardium. The precise role of the movement of calcium ions in the events that lead to irreversible myocardial cell death has not been completely defined, although considerable data[16] show that calcium deposition is a fundamental component of myocardial cell necrosis.

Local anesthetic agents have well documented membrane-stabilizing properties.[17,18] Presumably through membrane expansion, these agents increase the resistance of erythrocytes and erythrocyte ghosts to hypotonic hemolysis.[19,20] They decrease mitochondrial swelling by inhibition of phospholipase A and slow the flux of potassium and calcium across the mitochondrial membrane.[21,22] Schaub et al.[12] found that administration of lidocaine resulted in significant preservation of myocardial ultrastructure after normothermic ischemic arrest in the dog. Lidocaine limited mitochondrial swelling, sarcomere fragmentation and glycogen depletion. Boudoulas et al.[23] also found that lidocaine had a protective effect on the canine ischemic heart. This was associated with a negative inotropic effect on myocardial hemodynamic variables.

Thus, the purpose of this investigation was to answer the following questions: (1) What effect does the therapeutic serum concentration of lidocaine have on viability of ischemic myocardium? and (2) If lidocaine is protective, by what mechanism is this achieved?

Methods

Experimental protocol: Twenty-five mongrel dogs (10 to 14 kg body weight) were used: 12 control animals (group I), 8 dogs that received large doses of lidocaine (group II), and 5 that received small doses of lidocaine (group III). Each dog was anesthetized with thiamyl sodium (30 mg/kg body weight), and positive-pressure ventilation was maintained through an endotracheal tube. A left thoracotomy was performed through the fourth intercostal space. The thoracic contents were maintained at constant temperature with towels and by constant temperature of the environment. No radiant heat was used to the open chest area. The heart was suspended in a pericardial cradle, and a reversible ligature was placed around the left anterior descending artery 1 cm from its origin at the left coronary artery. The 40 minute occlusion phase was followed by 5 hours of reperfusion. The ligature was released during a 2 minute period. Ten minutes before the animals were killed, 2.5 ml of 10 percent α-zurine blue dye was injected into the femoral vein. The myocardium was stained with triphenyltetrazolium chloride, as described by J. T. Lie (personal communication).

The appropriate lidocaine concentrations were prepared in 500 ml of normal saline solution and infused continuously during a 340 minute period. Ten minutes before ligation, animals in groups II and III received an intravenous lidocaine bolus injection of 2 mg/kg, followed in group II by infusion of 0.2 mg/kg per min and in group III by infusion of 0.04 mg/kg per min during the occlusion and reperfusion phases. The control animals (group I) received a bolus injection of normal saline solution, followed by an infusion of normal saline solution throughout the experimental period.

Hemodynamic measurements: Instrumentation and placement of catheters were identical in all groups. In each preparation, a cannula (size 3F) was introduced into the inferior vena cava from the femoral vein, into the abdominal aorta from the femoral artery, into the left atrium from the atrial appendage, and into the left ventricle through the apex of the heart. The cannulas were connected to strain gauges, and recordings were made on a six channel Sanborn polygraph. Cardiac output was measured by the indocyanine green dye method, with recording of curves and computation of cardiac outputs on a Waters Instrument cardiac output computer. Hemodynamic variables (including aortic, left atrial and left ventricular pressures, first derivative of ventricular pressure [dP/dt] and cardiac output) were measured during coronary occlusion at 5, 20 and 40 minutes and during reperfusion at 5, 15, 30, 60, 120, 180, 240 and 300 minutes. Left ventricular stroke work was defined as the product of mean left ventricular systolic pressure and stroke volume. Arterial oxygen saturation was maintained at more than 90 percent by varying the respiratory rate, total volume and inspired oxygen concentration. The arterial pH was maintained between 7.3 and 7.4.

Mitochondrial studies: Isolation of cardiac mitochondria in our laboratory has previously been described.[24] The average yields of mitochondrial protein were significantly lower in the ischemic perfused myocardium, reflecting disruption of mitochondria concomitant with cell necrosis. The mitochondrial yields (mg/g of myocardium) from the ischemic samples were similar among the three groups: mean ± standard error of the mean 0.9 ± 0.3 in group I, 0.7 ± 0.3 in group II, and 0.8 ± 0.2 in group III, and 1.3 ± 0.4, 1.2 ± 0.3, and 1.4 ± 0.1, respectively, in the samples from normal myocardium.

The indexes of oxidative phosphorylation, as defined by Chance and Williams,[25] were characterized polarographically by the method modified from Sordahl et al.[26] The oxidative indexes were defined as follows: ADP:O = nmol of adenosine diphosphate (ADP) phosphorylated per natom of oxygen consumed; state 3 respiration = the rate of oxygen consumption during ADP phosphorylation; state 4 (the resting state) = rate of oxygen consumption after completion of ADP phosphorylation; and respiratory control index (RCI) = the ratio of state 3 to state 4 oxygen consumption ("tightness" of coupling of oxidation to phosphorylation). Although all indexes were determined, only the results of state 3 respiration will be given here because this index is the most sensitive to ischemic change.

Creatine kinase: Depletion of creatine kinase was estimated, as described by Kuby et al.[27] The specimens were placed in a homogenizing medium used for analysis of creatine kinase (0.25 mol/liter of sucrose in solution with 0.001 mol/liter of ethylenediaminetetraacetic acid [EDTA] sodium), homogenized in a Polytron homogenizer, and centrifuged in a Sorvall refrigerated centrifuge at a speed of 17,000 rpm for 10 minutes. Creatine kinase analysis was done on the supernatant. An aliquot was taken from the homogenized sample for the estimation of blood flow (see later) by analyzing the radioactivity in a well scintillation counter.

Myocardial blood flow: Myocardial blood flow was estimated 20 minutes after occlusion of the left anterior descending artery using strontium-85 microspheres. The mi-





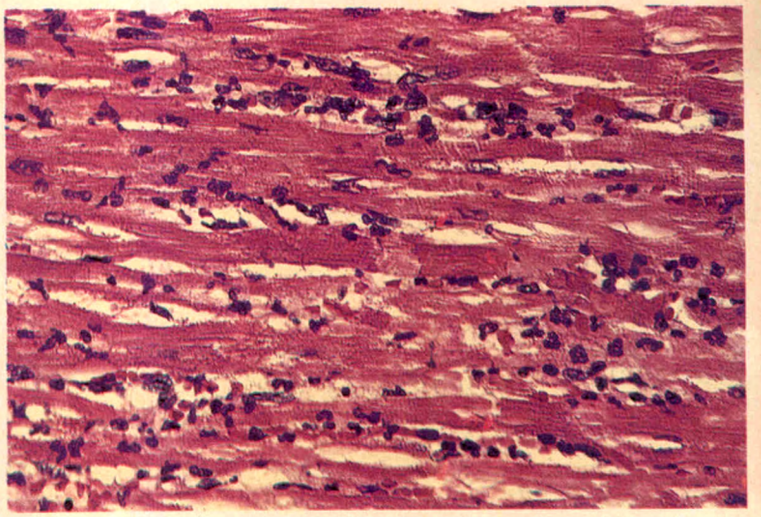


FIGURE 1. Gross and histologic sections of myocardium. **Upper left,** heart stained in vivo with α-zurine blue, demonstrating normal nonischemic myocardium. Nonischemic myocardium is colored blue. In border zones of hyperemia, a green stain is present. Infarcted nonperfused areas are red. These findings were confirmed by histologic study. **Lower left,** heart stained in vitro by triphenyltetrazolium chloride. The α-zurine blue disappears during the triphenyltetrazolium chloride staining. The nonischemic tissue stains red, and the pale tissue is necrotic. **Above,** section obtained from necrotic area of heart. Early necrosis with neutrophil infiltrate is seen. (Hematoxylin-eosin ×100, reduced by 20 percent.)

crospheres were placed under the ultrasonic beam for 30 minutes, then vigorously shaken by hand before injection. A polyvinyl catheter was placed in the left atrium through its appendage for the injection of the labeled microspheres, and another catheter was positioned in the femoral artery for the simultaneous withdrawal of reference blood samples.[28–30] Fifteen minutes after occlusion, 0.8 ml of solution containing the microspheres (8 to 10 μm in diameter, 3M Company, St. Paul, Minnesota) was injected into the left atrium during a period of 15 seconds. The catheter was flushed with 10 ml of normal saline solution during the next 15 seconds. Commencing 15 seconds before injection, blood was withdrawn from the femoral artery at a constant rate of 10 ml/min for 2 minutes. Myocardial blood flow (MBF) was calculated as follows: MBF (ml/g per min) = Reference blood flow (RBF) × 5 minute counts of 1 g of myocardium/Total RBF counts for 5 minutes, in which RBF = blood withdrawn from the femoral artery after injection of microspheres.

Estimation of infarct size: Several methods can be used in the experimental model for the histologic confirmation of cell necrosis. Kjekshus and Sobel[10] related total left ventricular depletion of creatine kinase to infarct size, expressed as a percent of left ventricular weight. Maroko et al.[5] related regional myocardial blood flow at 15 minutes after the ligation to creatine kinase depletion at 24 hours. J. T. Lie (personal communication) confirmed triphenyltetrazolium chloride myocardial stain as an in vitro marker of cell necrosis. We utilized similar methods. Triphenyltetrazolium chloride is a surface stain, and myocardial infarction is never homogeneous. To overcome this variable, an in vivo stain, α-zurine blue, was used to demarcate normal and necrotic tissue.[29,31,32] Intravenously in vivo injected α-zurine blue stains all perfused tissue an intense blue color (Fig. 1). Nonperfused necrotic tissue is unstained. A bolus injection of 2.5 ml of 10 percent solution of α-zurine blue was injected into the femoral vein 5 minutes before the animals were killed. This had no effect on hemodynamic variables. The excised myocardium was cut into slices of 0.5 cm thickness from apex to base and was macroscopically examined. The unstained and grossly necrotic tissue was separated from the stained normal myocardium by careful dissection along the blue border. Unstained tissue extending into the right ventricle was discarded.

In each heart with the left anterior descending artery ligated, the dye failed to penetrate the subendocardial layers and, to a various extent, the mid wall and sometimes even the epicardial layers. Because the absence of patent vessels apparently did not allow the dye to enter, absence of stain in this region was considered to indicate gross necrosis; this conclusion was supported by histologic examination (Fig. 1). A sample was obtained from the apparent center of the unstained region. This tissue sample, as well as a sample of normally perfused tissue from the posterior base of the left ventricle, was homogenized and assessed for its content of creatine kinase activity and mitochondrial function. Regional myocardial blood flow was estimated from an aliquot of this homogenized tissue. However, even in samples from the apparent center of the ischemic region, small amounts of normally perfused myocardium were found. This admixture of tissue can average up to 2.4 percent of the tissue of the sample.[33] Because of the tissue admixture at the border zone, this necessitated the use of triphenyltetrazolium chloride as an additional marker of cell death. The nonstained necrotic tissue and nonischemic blue-stained tissue were weighed. There was excellent correlation between the two stains.

Specimens were selected for histologic confirmation of cell necrosis. Tissue for histologic examination was processed and stained with hematoxylin-eosin and with Mallory-Heidenhain trichrome and was reviewed by one of us (W.D.E.), who had no knowledge from which group the specimen was obtained. In areas of discrepancy, in particular at the border zone, depletion of tissue creatine kinase was assayed, and if the creatine depletion was consistent with the infarcted area, this was added to the infarct weight. This method of dual staining allows accurate sampling of tissue and, when supplemented with estimation of tissue creatine kinase, excludes noninfarcted tissue from the estimation of infarct size.

Statistical analysis: All data were subjected to statistical analysis by computing mean and standard error. Paired Student's *t* tests for significant comparison were performed relative to the preocclusion control data and between measurements performed during occlusion and the reperfusion period. Data from individual experiments were studied in addition to the statistical mean trends. Data were considered significantly different when the probability (p) values were less than 0.05.

Results

All 25 dogs survived the ligation period, and 23 dogs survived the 5 hours of reperfusion. One dog treated with large doses of lidocaine and one control dog died with cardiogenic shock (that is, with a persistent reduction of more than 30 percent in both cardiac output and arterial systolic pressure 2 and 3 hours, respectively, after reperfusion). Data on these dogs were excluded from the results.

Infarct size: The infarcted tissue was expressed as a percent of total left ventricular weight. The amounts of infarcted tissue (in percent) were 12.6 ± 2.0 in group I, 4.8 ± 1.2 in group II ($p < 0.02$) and 4.8 ± 2.5 in group III ($p < 0.05$). Lidocaine produced an almost three-fold reduction in infarct size. Among the lidocaine-treated dogs, 1 (8 percent) had a myocardial infarct greater than 8.5 percent of the left ventricular weight, compared with 8 dogs (73 percent) in the control group. In the control group, 5 dogs (44 percent) had an infarct greater than 15 percent of left ventricular weight, compared with none for the lidocaine-treated groups.

Serum lidocaine levels: The mean serum concentration (μg/ml) of lidocaine 3 hours after reperfusion was 14.5 ± 2.2 in group II and 3.3 ± 0.6 in group III; the 5 hour value was 16.8 ± 2.0 in group II and 3.9 ± 1.2 in group III. The lidocaine serum levels were 3.8 μg/ml immediately after a 2 mg/kg bolus injection and 1.3 μg/ml 10 minutes after the same bolus injection. The bolus dose had no significant effect on preocclusion coronary hemodynamics.

Cardiac arrhythmia: Transient arrhythmias were most common during the occlusion phase and, in particular, immediately after reperfusion. Persistent supraventricular tachyarrhythmias were uncommon in all groups. However, ventricular premature systoles and ventricular tachyarrhythmias were most common in the control group. Sudden reperfusion is a potent method to induce malignant arrhythmias. Atrioventricular dissociation with a slow ventricular pacemaker was noted in two dogs in the group treated with large doses of lidocaine; in both groups, the episodes occurred during the last hour of reperfusion.

Hemodynamics: Data regarding cardiac rate, dP/dt and stroke work are given in Figure 2.

Mean aortic pressure: At the end of 40 minutes of occlusion, the mean aortic pressure was reduced below the preocclusion control level to an average of 30, 26 and 25 percent, respectively, in the three groups. Reperfusion caused a further respective reduction of 30, 55 and 27 percent. Mean aortic pressure was significantly lower in group II than in groups I and III after 3 1/2 hours of reperfusion.

Left ventricular end-diastolic pressure: The left ventricular end-diastolic pressure in the group treated with large doses of lidocaine was significantly greater than that in the control group at 240 and 300 minutes of reperfusion.

Maximal rate of rise of left ventricular pressure (dP/dt): This index decreased acutely during occlusion in all groups. At the end of reperfusion, maximal left ventricular dP/dt was significantly lower in the group treated with larger doses of lidocaine than in groups I and III at 30, 50, 120, 180, 240 and 300 minutes of reperfusion.

Left ventricular stroke work: Coronary occlusion caused a decrease of 36 to 61 percent in left ventricular stroke work in all dogs. During reperfusion, stroke work continued to decrease in all three groups, but there were no significant differences among the three groups during either the occlusion or the reperfusion phase.

State 3 respiration: In the three groups, the mean state 3 respiratory rate in the ischemic reperfused endocardium was significantly less than in the nonischemic myocardium with either glutamate or succinate-rotenone as substrate. The percent of depression in state 3 respiration in the ischemic myocardium with glutamate as substrate was 73 percent in both groups I and II and 53 percent in group III (Table I).

State 3 respiratory indexes with succinate-rotenone as substrate paralleled those with glutamate as substrate. Small dose lidocaine (in group III) was associated with a higher state 3 respiratory rate with use of both substrates after 40 minutes of ischemic occlusion and 5 hours of reperfusion, but because of the great variability in the rates the difference was not significant.

Effect of reperfusion on mitochondrial function: State 3 respiratory functions in reperfused and nonreperfused ischemic and nonischemic endocardium in

TABLE I

State 3 Respiratory Rates* in Myocardium Using Glutamate as Substrate

Biopsy Tissue	Group I	Group II	Group III
Chest open 340 minutes (nonischemic)	180 ± 13	160 ± 13	150 ± 8
Reperfused ischemic endocardium (40 minutes of ligation, 5 hours of reperfusion)	48.3 ± 13	43.6 ± 9	71.3 ± 31

* Respiratory rate (mean ± standard error of the mean) in natoms oxygen/mg protein per min.

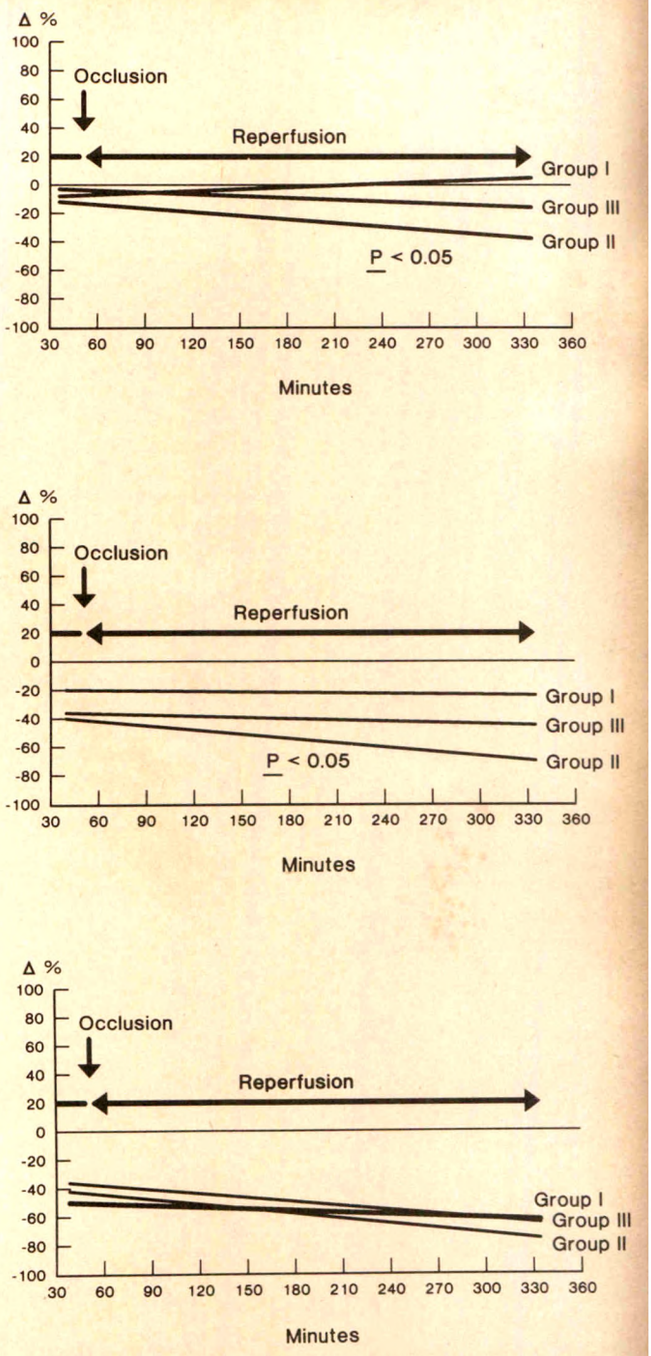


FIGURE 2. Hemodynamic variables. Data points are not shown; only regression lines (Δ%) are present. **Top,** heart rate in group I (control), group II (large dose lidocaine) and group III (small dose lidocaine). The percent change is from the control rate (that is, the rate before occlusion [**vertical arrow**] of the left anterior descending coronary artery). The heart rate in group II was significantly ($p < 0.05$) different from that in the control group. **Middle,** first derivative of left ventricular pressure (dP/dt) expressed as percent change from the value obtained before occlusion of the left anterior descending coronary artery. Values in the dogs treated with large dose lidocaine (group II) were significantly ($p < 0.05$) different from those in the control dogs (group I). No significant difference was found between the control group and dogs treated with small dose lidocaine (group III). **Bottom,** left ventricular stroke work (left ventricular mean pressure × stroke volume) expressed as percent of preocclusion value. No significant differences were found among the three groups.

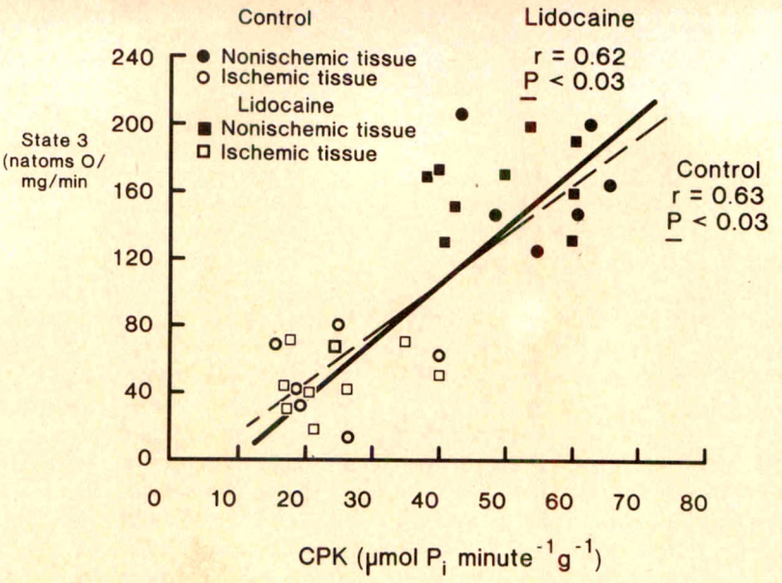


FIGURE 3. Oxygen consumption of mitochondria after the addition of adenosine diphosphate (state 3, glutamate substrate) expressed in natoms oxygen/mg per min plotted against myocardial creatine kinase (30° C incubation) in the same biopsy specimen obtained from control nonischemic and ischemic tissue and from lidocaine-treated nonischemic and ischemic tissue. A significant relation was found between state 3 respiration and myocardial creatine kinase in both ischemic and nonischemic tissue. Note the significant difference ($p < 0.001$) between the creatine kinase values from ischemic tissue (**open circle and square**) and the values from nonischemic tissues (**closed circle and square**).

the control and lidocaine-treated dogs are given in Table I. With glutamate as substrate, the state 3 respiratory rate for normal endocardium in our laboratory is 170 ± 20 natoms oxygen/mg per min.

Reperfusion for 5 hours had a further deleterious effect on the respiratory function in all groups, with a reduction of 21 percent in state 3 respiratory function in the control group and of 44 percent in the group treated with large dose lidocaine. Five hours of reperfusion after 40 minutes of ligation did not improve state 3 respiratory function with or without lidocaine.

Relation between creatine kinase and state 3 mitochondrial respiration: A linear relation was found between state 3 respiratory function and creatine kinase level in the myocardium. This was true for both ischemic and nonischemic myocardium with and without lidocaine infusion (Fig. 3). The creatine kinase levels in normal and necrotic tissues were similar in the three groups, 50 and 36 μmol, respectively, of inorganic phosphorus/min per g of myocardium at 30° C.

TABLE II

Regional Myocardial Blood Flow*

Tissue	Group I	Group II	Group III
Normal	98.85 ± 13.08	110.8 ± 12.92	88.0 ± 16.7
Ischemic	6.40 ± 1.7	1.48 ± 0.006	1.32 ± 0.008

* Mean ± standard error of the mean, measured in ml/min per 100 g of tissue; normal range 80 to 160. A reduction of 90 percent or more in normal myocardial blood flow in the ischemic region was achieved in all groups.

Creatine kinase levels in tissues from the centers of necrotic zones were significantly ($p < 0.001$) lower than levels in nonischemic tissue. Because the creatine kinase concentrations were measured in the centers of the necrotic zones, no difference was found between the control and lidocaine-treated dogs.

Regional myocardial blood flow: Data regarding regional blood flow are given in Table II.

Discussion

Various pharmaceutical preparations have been cited in recent years as reducing the acute effects of ischemia on the myocardium. Although the electrophysiologic effects of lidocaine have been thoroughly investigated, this drug's effect on ischemic cell viability has until recently received little attention.

Determinants of extent of myocardial necrosis: In severe acute myocardial ischemia, cell death occurs earliest in the subendocardial zone, and about one half of the ischemic myocardium that is necrotic at 24 hours has already died by 40 minutes.[34] Cell death occurs more slowly in the mid myocardium and subepicardium, so that on the average about half of the ischemic myocardium at risk is still salvageable at 40 minutes. Interventions for the salvaging of these jeopardized ischemic myocardial cells, when they are still in the reversibly injured phase, can decrease the size of the infarct. Previous techniques using electrocardiographic variables as an index of myocardial protection have become a subject of some controversy.[35–40] Regional myocardial blood flow after coronary occlusion is a reliable predictor of later cell death.[41–43] A close relation exists between

the ischemic level of blood flow and the subsequent depletion of creatine kinase 24 hours after occlusion in the transmural tissue samples from the ischemic region, as well as in the samples from the subendocardial and subepicardial halves.[43] This finding suggests that the initial residual perfusion of the ischemic region is a major determinant of the subsequent extent of myocardial necrosis and emphasizes that the tissue flow existing early after occlusion is the primary determinant of the ultimately emerging infarct size.[4,33]

Lidocaine for preservation of ischemic myocardium: Previous investigations have suggested that lidocaine may have a salutary effect on myocardial cell preservation.[23,44] Although the specific mechanisms of the action of local anesthetic agents are unknown, it is generally accepted that an interaction of the drugs with some component of the cell membrane is involved.[21,45–51] Local anesthetic agents may affect a specific site on the mitochondrial membrane involved in potassium transport, inhibiting potassium efflux as well as the calcium-hydrogen exchange. Injury to ischemic tissue is associated with extreme changes in intracellular ionic concentration.[6,52,53] The rapidity and magnitude of changes in water and electrolytes of injured myocardium suggest that defects in the sarcolemmal membrane may be of primary importance in the pathogenesis of irreversible cell injury. Fifteen minutes of ischemic occlusion, a reversible insult, causes only a slight increase in intracellular sodium content. This alteration is in marked contrast to the changes after an irreversible ischemic insult of 40 minutes. These ischemic myocardial cells after 2 minutes of reperfusion manifest an increase of 40 percent in intracellular sodium and chloride content and an increase of 100 percent in intracellular calcium content. Concomitant with these changes is the efflux of potassium and magnesium.[6] Local anesthetic agents stabilize the electrophysiologic cell membrane, thereby maintaining ionic homeostasis, and this may decrease the pathologic electrolyte changes caused by ischemia and may provide a milieu that is more supportive for the viability of jeopardized ischemic myocardial cells.

Mechanisms of lidocaine's beneficial effect: These experiments demonstrated a decrease in mitochondrial state 3 respiratory rate after 40 minutes of ligation of the left anterior descending coronary artery, followed by 5 hours of reperfusion. The amount of necrosis in the ischemic tissue in the groups treated with lidocaine was only one third of that in the control group, even though the lidocaine-treated groups had slightly less myocardial blood flow. Creatine kinase depletion in the ischemic areas was not significantly different in the three groups, because the creatine kinase determinations were obtained from the centers of the infarcts. The linear relation of state 3 mitochondrial function to creatine kinase depletion relates oxidative phosphorylation to the creatine kinase concentration in myocardial ischemic tissue.

In all groups, the hemodynamic variables failed to return to the preischemic level after 5 hours of reperfusion of the ligated artery. Highly toxic concentrations of lidocaine further depressed hemodynamic variables. The dose utilized (16.8 μg/ml) was five times greater than the normal dose used in clinical application. This large dose was administered to assess whether lidocaine protection of the ischemic myocardial cell was due to a negative inotropic effect. This large dose would also decrease myocardial oxygen consumption. Previous work[23,54] suggested that this reduction of oxygen utilization was the mechanism of myocardial preservation by lidocaine. However, our data do not support this conclusion, because in the small dose group there was a similar salutary effect on myocardial cell viability without depression of myocardial work.

The lowest mean level of regional myocardial blood flow was in the lidocaine-treated groups, that in group III being the lowest. Because the initial residual perfusion of the ischemic region is a major determinant of the subsequent extent of myocardial necrosis, the lidocaine-treated groups would have been expected to have the more extensive tissue necrosis. Lidocaine had a beneficial effect on myocardial preservation in a therapeutic serum concentration despite a lower level of regional myocardial blood flow. The mechanism of tissue preservation by lidocaine was not by negative inotropism or by a significant improvement of cardiac rhythm in these experiments. Local anesthetic inhibition of membrane electrolyte flux, in particular that of potassium and calcium, may offset the increased permeability of the ischemic myocardial cell and, in some manner, produce a milieu that is more appropriate to ischemic myocardial cell preservation. Lidocaine may be beneficial not only in its antiarrhythmic effect[55] but also in its salutary effect on myocardial cell preservation.

Clinical implications: Pretreatment with lidocaine is not needed to decrease infarct size[23] or to permit lidocaine to reach the ischemic zone.[56] Boudoulas et al.[23] infused lidocaine 30 minutes after ligation of the left anterior descending artery, and this had a significant beneficial effect in decreasing ischemic injury in dogs. They also reported a reduction in the sum of S-T elevation in patients with anterior myocardial infarction. These patients were not pretreated with lidocaine. Moreover, pretreatment is not necessary for lidocaine to reach the ischemic zone. As reported by Weintraub et al.,[56] carbon-14–labeled lidocaine infused after ligation of the left anterior descending artery diffused into the ischemic zone. Lidocaine was concentrated 2.2-fold relative to ischemic myocardial blood flow, whereas in the nonischemic zone lidocaine was concentrated equivalent to myocardial blood flow. The tissue concentration of lidocaine was higher in the ischemic endocardium than in the ischemic epicardium, suggesting diffusion of lidocaine from cavitary blood to endocardium in the ischemic zone. Thus, lidocaine therapy for preservation of ischemic myocardial cells could potentially be given to patients who have acute coronary insufficiency before or early in the course of myocardial infarction.

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Comparison of Multigated Radionuclide Angiography With Ultrasonic Sonomicrometry Over a Wide Range of Ventricular Function in the Conscious Dog

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This study compared the noninvasive assessment of left ventricular function with radionuclide angiography with that obtained with ultrasonic sonomicrometry. Left ventricular ejection fraction and rate of ventricular ejection (dV/dt) were measured with both techniques over a wide range of ventricular function. Six dogs were prepared with epicardial crystals across the major and minor axes of the left ventricle, paired transmural wall thickness crystals and a left ventricular catheter. The animals were studied while awake after they had recovered from operation. Left ventricular volume was calculated from the ultrasonic sonomicrometric dimension measurements and the equation for a prolate ellipsoid; dV/dt was calculated from the stroke volume and ejection time. Radionuclide angiograms were performed using technetium-99m–labeled red blood cells and an Anger camera with a converging collimator interfaced to a computer programmed for multigated acquisition.

A wide range of ventricular function was produced with sequential infusion of isoproterenol, propranolol, phenylephrine and sodium thiamylal. Ejection fraction and dV/dt were measured simultaneously during each intervention using the time-activity curves of the multigated radionuclide angiogram and ultrasonic sonomicrometric dimensions. Regression analyses demonstrated a close correlation between the simultaneous measurements of ejection fraction (r values ranged from 0.95 to 0.99) and dV/dt (r values ranged from 0.87 to 0.99). These data indicate that noninvasive multigated radionuclide angiography accurately assesses changes in ejection fraction and dV/dt over a wide range of ventricular function.

Multigated radionuclide angiography is a widely used technique for noninvasively assessing left ventricular function. Appropriate use of this technique to evaluate sequential changes in ventricular function requires that it be validated with respect to accuracy and reproducibility. Previous studies[1–6] have compared radionuclide and contrast angiographic measurements of ejection fraction in groups of patients and have reported correlation coefficients ranging from 0.80 to 0.97. The potential limitations of such studies include the inability to record measurements simultaneously, the direct effects of contrast material on ventricular function, and the inability to perform serial measurements or assess a wide range of ventricular function in the same patient.

This study compared indirect noninvasive measurements of ventricular function with radionuclide angiography with measurements of left ventricular dimension using ultrasonic sonomicrometry. The ultrasonic sonomicrometric technique has the advantage of providing precise direct measurements of ventricular dimensions that can be obtained in a continuous beat to beat fashion.[7] These techniques provided repeated simultaneous measurements over a wide range of ventricular function in each animal.

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Methods

Experimental Preparation (Fig. 1)

Sonomicrometric system: Six mongrel dogs weighing between 20 and 40 kg were anesthetized with sodium thiamylal (30 to 40 mg/kg body weight) and underwent left lateral thoracotomy. A 3 mm polyvinyl chloride catheter filled with heparin was inserted into the left ventricular cavity through a stab wound through the apex of the heart. Two 5 mm piezoelectric epicardial ultrasonic dimension transducers were sutured across the minor axis of the heart, one to the anterior free wall of the left ventricle and the other to the posterior free wall midway between the apex and the base of the heart. Two additional dimension transducers were sutured across the major axis of the heart, one to the epicardium at the apical dimple and the other to the base of the heart in the groove between the left sinus of Valsalva and the left atrium, overlying the fibrous continuity between the aortic and mitral valves. Left ventricular anterior wall thickness was measured by passing an ultrasonic crystal, 2 mm in diameter, through the myocardium to the depth of the endocardium. A second transducer was then sutured to the epicardium directly over the endocardial crystal. The chest incision was then closed and the catheter and wires tunneled to a dorsal subcutaneous pouch at the base of the neck. The animals were allowed to recover for 7 to 10 days before being studied.

On the morning of the study, each animal was given 10 to 20 mg of morphine sulfate intramuscularly and was studied while lying loosely restrained on its right side. The subcutaneous pouch was infiltrated with 1 percent lidocaine hydrochloride and the catheter and wire leads were brought out through a small incision. The left ventricular pressure catheter was connected to a Statham P23Db transducer (Statham Instruments, Inc., Oxnard, California), and the zero reference was taken at the mid chest level. The three pairs of ultrasonic pulse transducers were connected to a sonomicrometer. The system converts the transit time of a pulse of ultrasound between two piezoelectric transducers into an analog signal. Because the velocity of sound in body tissues and blood is constant, the measured transit time is directly proportional to the distance between the transducers. The sonomicrometer was calibrated by substituting an electronically generated time delay into the circuitry. Each channel of the sonomicrometer was pulsed sequentially to eliminate cross interference. The measured electronic drift was less than 0.05 mm/hour, and the relation between crystal separation and voltage output was linear over the ranges encountered in this study. The minimal resolution of the sonomicrometer-transducer system of 0.05 mm provided data for very precise dimension measurements.

Radionuclide angiography: Multigated radionuclide angiograms were recorded after red cells were labeled in vivo with 30 millicuries (mCi) of technetium-99m using the method of Pavel et al.[8] Radionuclide angiograms were acquired using a Searle L.E.M. mobile scintillation camera with a converging collimator and an R wave triggered gate interfaced to a Medical Data Systems PAD computer. Studies were acquired in histogram mode in a 32 by 32 matrix of 56 frames of 50,000 counts each. Studies were acquired in sequential pairs.

Studies were first carried out in dogs not included in the present analysis to determine the imaging position for optimal separation of the left ventricular chamber from surrounding structures. Radioactive markers were sutured to the left atrioventricular ring in the anterior, lateral and inferior portions. Images were recorded before and after labeling of the blood pool. The ventral position with slight caudal tilt and the collimator parallel to the frontal plane produced optimal left ventricular separation. With this degree of caudal tilt the lower portion of the left atrium overlays the upper one-fourth of the left ventricular image (Fig. 2).

Protocol: A wide range of left ventricular function was produced by sequential infusion of isoproterenol 2 to 6 μg/min, propranolol 0.8 to 1.0 mg/kg, phenylephrine 100 to 200 μg/min, and finally increasing doses of sodium thiamylal to severely depress function in each dog. Ultrasonic dimensions, left ventricular pressure and heart rate were recorded continuously during the study. During each intervention simultaneous radionuclide angiograms and dimension measurements

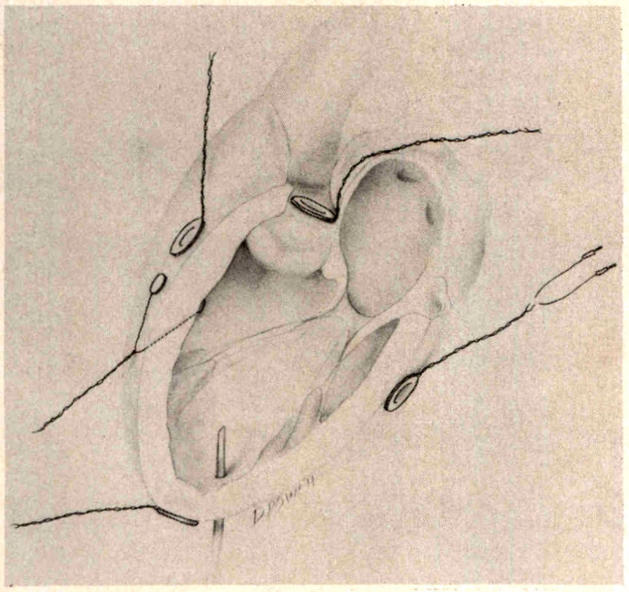


FIGURE 1. Drawing of the surgical preparation. Ultrasonic transducers are positioned to measure left ventricular major and minor axis diameters and wall thickness. The apical catheter is inserted to measure left ventricular pressure.

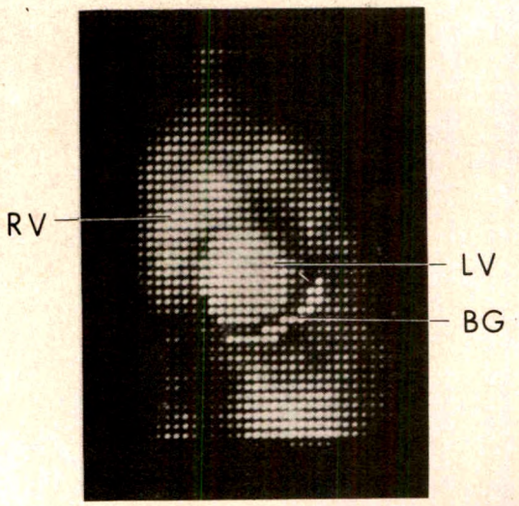


FIGURE 2. Photograph of the radionuclide cardiac image in the anterior projection with slight caudal tilt. BG = background; LV = left ventricle; RV = right ventricle.

were obtained, and most measurements were obtained in duplicate. This resulted in 7 to 14 data acquisitions for each animal. At the end of the study each animal was killed, the heart was removed and the six ultrasonic transducers were checked to assure correct positioning.

Ejection fraction measurements as a function of time: Additional studies were performed in a separate group of dogs that were not subjected to operation to determine the variability of the ejection fraction in intact dogs as a function of time. Radionuclide angiograms were recorded a minimum of 7 days apart in a group of 10 dogs. Two to three radionuclide angiograms were recorded in each dog in the same manner as previously described. The animals were studied in the awake state; no sedation was used.

Data Analysis

Radionuclide angiography: The multigated radionuclide studies were interpolated into a 64 by 64 matrix and adjacent frames were added to produce 28 frame studies of 100,000 counts/frame. Left ventricular ejection fraction was evaluated using a varying region of interest technique. Regions were assigned using an operator-assisted semiautomatic edge detection program (MUGE). This program was used to assign a region of interest to describe the left ventricle for each frame of the study. Analysis of counts in each region allows the construction of a time-activity curve and determination of the ejection fraction and rate of ventricular ejection (dV/dt). The volume curve was corrected for background by subtracting average background counts/pixel in each region for each frame of the curve. Average background was determined by using a light pen to assign a region of interest adjacent to and inferiorly and laterally to the end-systolic left ventricular region of interest, taking care to exclude the liver and descending aorta (Fig. 2). The background region was approximately 2 pixels lateral to the ventricular region of interest and was 2 to 3 pixels wide. End-diastole (ED) and end-systole (ES) were determined from the peak and trough of the time-activity curve, respectively.

Ejection fraction (EF) was calculated by the formula: EF = (End-diastolic counts − background) − (End-systolic counts − background)/(End-diastolic counts − background).

Average dV/dt was calculated by the first derivative of the volume curve using the formula:

$$dV/dt = \frac{\int_{ED}^{ES} V'(t)dt}{\frac{ES - ED}{counts/EDV}},$$

where V′(t) = the first derivative of the volume curve; ES and ED = the time after the R wave of end-systole and end-diastole, respectively; and counts/EDV = counts/end-diastolic volume. ES − ED represents the left ventricular ejection time. Because the absolute volume of the left ventricle was not determined with gated angiography in these experiments, dV/dt can not be expressed in cc/s. However, dV/dt can be expressed as a function of the end-diastolic volume by normalization with the counts/end-diastolic volume. The resulting units are EDV/s. Peterson et al.[9] observed that mean normalized systolic ejection rate expressed as EDV/s was useful for differentiating patients with normal and abnormal ventricular function. Hammermeister et al.[10] concluded that correcting dV/dt for different end-diastolic volumes improved the index as a descriptor of ventricular function.

Sonomicrometry: A representative analog recording of left ventricular pressure and ultrasonic dimensions is shown in Figure 3. Left ventricular major axis, minor axis, and wall thickness dimensions were determined at end-diastole and end-systole. End-diastole and end-systole were determined from the left ventricular pressure tracing and the configuration of the dimension recordings. At least 10 consecutive beats were used to measure systolic and diastolic dimensions for each acquisition. The geometry of the left ventricle was assumed to be that of a prolate ellipsoidal shell.

Previous studies have demonstrated that calculations of ventricular volume from the prolate ellipsoidal model and sonomicrometric dimension measurements were comparable with postmortem measurements of volume and measurements of stroke volume using aortic flow probes.[11] The internal volume of the left ventricle was calculated at end-systole and end-diastole using the formula: $V = \pi \div 6\,(b - 2h)^2\,(a - 1.1h)$, where b = the external minor axis diameter; h = the equatorial

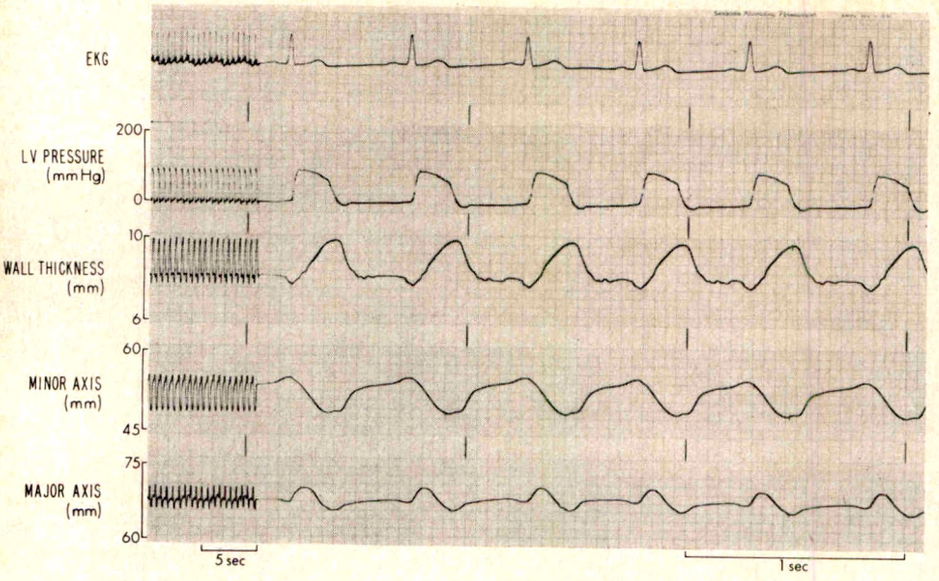


FIGURE 3. Analog recording of the ultrasonic dimension measurements and left ventricular (LV) pressure. EKG = electrocardiogram.

wall thickness; and a = the external major axis diameter. Ejection fraction was calculated by dividing stroke volume by end-diastolic volume. The average dV/dt for the cardiac cycle was calculated by dividing the stroke volume, obtained from the end-diastolic and end-systolic volumes, by the ejection time. This value was normalized for the end-diastolic volume (EDV) of each measurement and expressed in units of EDV/s for comparison with the radionuclide data.

The radionuclide angiographic and sonomicrometric measurements were determined independently by investigators who were unaware of each other's results.

Results

Degree of alteration of ventricular function: The ranges of ejection fraction and rate of ventricular ejection (dV/dt) produced by the various drug interventions in each dog are listed in Table I. Comparisons were made over a wide range of ejection fraction and dV/dt in each animal. The average ejection fraction ranged from 19 to 48 percent with sonomicrometry and from 30 to 67 percent with radionuclide angiography. The average dV/dt ranged from 1.24 to 3.07 EDV/s with sonomicrometry and from 1.17 to 4.36 EDV/s with radionuclide angiography.

Reproducibility of paired acquisitions: In each animal, duplicate acquisitions of both sonomicrometric and radionuclide angiographic data were made during each intervention at steady state conditions. The reproducibility of each method was determined from the difference between duplicate measurements. The variability in ejection fraction of paired acquisitions was 2 ± 0.5 percent with sonomicrometry and 3 ± 0.6 percent with radionuclide angiography. The variability of paired measurements of dV/dt was 0.13 ± 0.02 EDV/s with sonomicrometry and 0.27 ± 0.13 EDV/s with radionuclide angiography. The variability of paired acquisitions was greatest at the lower ranges of ejection fraction and dV/dt in each animal.

Ejection fraction: Regression analyses between ejection fraction measurements with sonomicrometry and radionuclide angiography demonstrated a close linear relation in each animal, with individual correlation coefficients ranging from 0.95 to 0.99 (Fig. 4). The linear regression equations describing the relation between sonomicrometric and radionuclide angiographic ejection fraction in the individual animals had slopes greater than 1 and Y intercepts greater than 0. The ejection fractions measured with radionuclide angiography tended to be greater than those measured with sonomicrometry and the difference increased as the ejection fractions increased. Therefore, in general, radionuclide angiographic measurements overestimated the ejection fraction by comparison with sonomicrometric measurements and the overestimation increased as ejection fraction increased.

Ejection rate: The relation between dV/dt measured with sonomicrometry and that measured with radionuclide angiography in individual animals is shown in Figure 5. Regression analysis between sonomicrometric and radionuclide measurements demonstrated a close linear correlation in each animal; the correlation coefficients ranged from 0.87 to 0.99. The slopes greater than 1 demonstrate a relative overestimation of normalized dV/dt by radionuclide angiography in comparison with sonomicrometry.

TABLE I

Alteration in Ventricular Function Produced in Individual Animals

	Sonomicrometry		Radionuclide Angiography	
Dog	EF (%)	dV/dt (EDV/s)	EF (%)	dV/dt (EDV/s)
1	16–44	1.28–2.95	27–63	1.04–3.11
2	33–62	1.93–3.76	29–63	1.69–4.56
3	16–48	0.96–2.83	23–63	0.97–3.75
4	27–68	1.78–5.02	38–86	1.27–7.00
5	9–34	0.49–2.15	24–66	0.91–4.16
6	14–31	0.98–1.73	37–63	1.15–3.58
Mean	19–48	1.24–3.07	30–67	1.17–4.36

dV/dt = first derivative of ventricular volume (rate of ejection); EDV = end-diastolic volume; EF = ejection fraction, s = seconds; t = time.

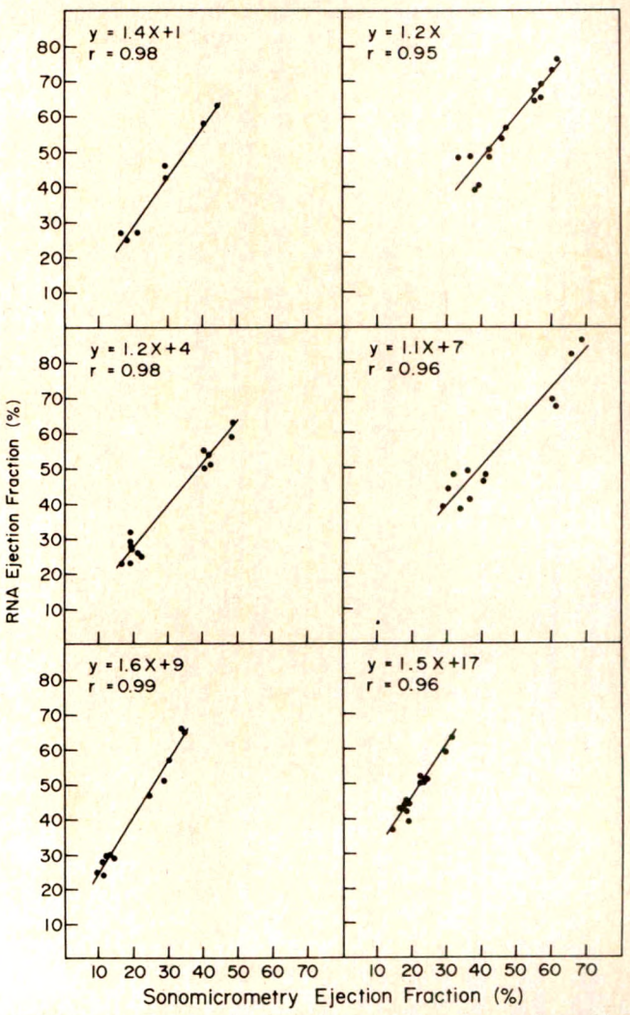


FIGURE 4. Ejection fraction by sonomicrometry versus radionuclide angiography (RNA) in six animals. The mean correlation coefficient (r) = 0.97 for the group.

Ejection fraction measurements as a function of time: In a group of dogs not subjected to surgery, initial and repeated ejection fraction measurements obtained with radionuclide angiography 7 or more days apart were comparable; the mean difference was 2.4 ± 2.2 percent standard deviation (Table II). In six of the dogs, the mean ejection fraction on different days differed by 1 percent or less.

Discussion

Accuracy of ultrasonic sonomicrometry for assessing left ventricular function: The objective of this study was to examine the ability of radionuclide angiography to assess changes in ejection fraction and ejection rate over a wide range of ventricular function in individual subjects. In previous studies,[1–6] the radionuclide angiographic measurements were compared with contrast ventriculographic measurements. There are several potential problems with using contrast angiography as a reference method. Contrast angiography is an invasive technique that can directly alter ventricular function. It is not feasible to inject contrast medium repeatedly in the same patient or to record the radionuclide and contrast angiograms simultaneously.

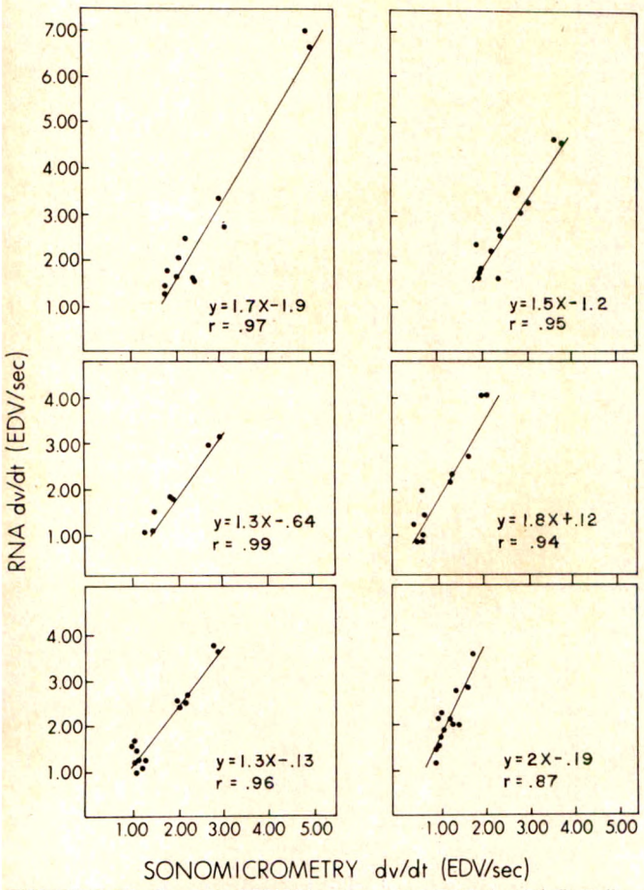


FIGURE 5. Ejection rate (dV/dt) by sonomicrometry in end-diastolic volume per second (EDV/sec) versus dV/dt by radionuclide angiography (RNA) in end-diastolic volume per second. The mean correlation coefficient (r) = 0.95 for the group.

The use of ultrasonic sonomicrometry as a reference method eliminates these potential problems. The implanted transducers provide a continuous beat to beat record of ventricular dimensions. Multiple sequential and simultaneous measurements of ventricular function can be obtained from the sonomicrometric and radionuclide angiographic measurements. Our investigation performed in conscious dogs provides a model for studying a wide range of ventricular function produced by drug infusion. The technique of ultrasonic sonomicrometry has previously been described[11] and has been validated by comparison with aortic blood flow and postmortem dimension measurements.[7] Ultrasonic sonomicrometry uses the same geometric assumptions as angiography, and it provides direct measurements of major and minor axes and wall thickness with a resolution of 0.05 mm[7] and thus provides a method that has a high degree of precision for assessment of changes in left ventricular function by radionuclide angiography.

Factors affecting ejection fraction measurements by sonomicrometry and radionuclide angiography: In our study, measurements of ejection fraction and rate of ventricular ejection (dV/dt) with sonomicrometry and radionuclide angiography over a wide range of ventricular function were highly reproducible. Regression analysis demonstrated a close linear relation between the measurements of ejection fraction with the two techniques; the linear correlation coefficient was 0.95 or greater in each animal. Although re-

TABLE II

Ejection Fraction Measurements as a Function of Time

Dog	Ejection Fraction (%) 1	2	3	Mean
1				
A	50	51	47	49
B	48	49	47	48
2				
A	61	60	61	61
B	60	60	61	60
3				
A	67	70		69
B	67	68	68	68
4				
A	61	61		61
B	59	60	61	60
5				
A	55	52	53	53
B	55	53	52	53
6				
A	56	58	57	57
B	52	52	54	53
7				
A	57	54		56
B	50	52		51
8				
A	52	60	61	58
B	57	59	58	58
9				
A	65	65	66	65
B	60	60		60
10				
A	72	72	75	73
B	68	67	66	67

A = initial measurements; B = measurements a minimum of 7 days later.

gression analysis demonstrated an excellent linear correlation between the noninvasive and direct measurements of ejection fraction, the slope of the regression equation was greater than 1 in most animals. Radionuclide angiography overestimated the ejection fraction measured with sonomicrometry and the magnitude of the overestimation increased as the ejection fraction increased (Table I, Fig. 4).

Several factors in the measurement of the ejection fraction with radionuclide angiography or sonomicrometry, or both, may have contributed to the discrepancy between the measurements. Measurement of the precise ejection fraction with radionuclide angiography requires accurate selection of the left ventricular region of interest and precise background assignment. Inclusion of nonventricular structures in the end-diastolic frame or overestimation of background activity, or both, would result in overestimation of the actual ejection fraction. Although the optimal separation of the left ventricular image was obtained in the anterior projection with a slight caudal tilt, it was not possible to exclude completely the lower portion of the left atrium from the diastolic image. Because of anatomic differences between the chest of the dog and that of human beings, the usual background algorithm of the computer software could not be used in this study. The automated background regions were often too large, sometimes extending beyond the thoracic cavity and often including the liver and descending aorta. Therefore, the background region of interest was assigned with a light pen in an area that appeared to be most analogous to that used in human studies (Fig. 2). This method resulted in highly reproducible measurements of ejection fraction. However, as can be seen from the formula for ejection fraction, if the background assignment method resulted in a systematic overestimation of the actual background, the calculated ejection fraction, although reproducible, would be higher than the actual ejection fraction. In addition, the degree of overestimation would be larger at higher ejection fractions. These changes would occur because, as ventricular volume decreases during systole, the average count/pixel in the ventricular region of interest decreases whereas background counts/pixel remain constant. As the target to background ratio decreases, overestimation of background would result in a relatively greater underestimation of actual systolic counts than of actual diastolic counts, thus increasing the apparent ejection fraction. The discrepancy between actual and apparent ejection fraction would become greater as the difference in target to background ratio between end-diastole and end-systole increased (that is, as the actual ejection fraction increased). A systematic overestimation of background would produce a regression plot showing an excellent correlation coefficient and high reproducibility but a regression equation with a positive Y intercept and a slope greater than 1.0.

Other potential limitations of sonomicrometry: In this study, the calculation of ejection fraction by sonomicrometry assumes that the left ventricle conforms to a prolate ellipsoid not only at normal function but also over the wide range of heart size and ventricular function produced in the study. The positioning of the wall thickness transducers is critical. An error as small as 2 mm in wall thickness determination can result in an error of 20 percent in volume determination.[8] The positioning of the major and minor axis transducers is less critical. A 2 mm error in positioning these transducers results in a less than 5 percent error in volume estimation.[8] The accuracy of sonomicrometry also depends on the absolute volume of the heart. Previous studies have demonstrated that in a given ventricle sonomicrometric measurements tend to overestimate slightly the actual volume of the small or normal ventricle and to underestimate that of the enlarged ventricle.[8] Therefore, underestimation of end-diastolic volume and overestimation of end-systolic volume would result in underestimation of the ejection fraction. Finally, it is possible that the geometry of the depressed and afterload-stressed ventricle is not defined by a prolate ellipsoid. Thus, several factors may have contributed to measurement differences with the two techniques. Nevertheless, our study demonstrates that the changes in ejection fraction determined with sonomicrometry result in proportional changes in ejection fraction determined with radionuclide angiography. These studies indicate that radionuclide angiography is a reliable technique for assessing the effects of interventions on ventricular function.

Measurements of ejection fraction a minimum of 7 days apart in the group of animals not subjected to surgery demonstrated very little variation in ejection fraction as measured with radionuclide angiography; the mean difference was 2.4 ± 2.2 percent (Table II).

Rate of ventricular ejection (dV/dt): This is another variable that may be used as an index of ventricular function. In this study, the dV/dt measurements were reproducible and there was a close linear relation between radionuclide angiography and sonomicrometric measurements in the ejection rate in each animal. Because absolute ventricular volumes were not determined with radionuclide angiography in this study, dV/dt was not calculated in units of absolute volume but was expressed as a function of end-diastolic volume.

Previous electromagnetic flow probe studies: In a recent study, Green et al.[12] used electromagnetic flow probes and multigated radionuclide angiography to measure simultaneously left ventricular systolic timing and relative volume variations. They observed a close correlation between the shape of the scintigraphic time-activity curves during systole and the equivalent curves synthesized from the aortic flow profile. No significant difference was observed between the time to peak aortic flow, time to cessation of the aortic flow and duration of aortic flow as measured with both techniques. Measurements were made during a single level of normal ventricular function in anesthetized dogs; the ejection fraction was not measured.

Implications: Our study demonstrates that ejection fraction determinations obtained with radionuclide angiography are reproducible and that, although radionuclide angiography overestimates ejection fraction

in comparison with sonomicrometry, an excellent linear correlation exists between the two techniques. A good linear correlation was found between the measurements of dV/dt with the two methods. The variation in ejection fraction measured on different days with radionuclide angiography was very small. Radionuclide angiography is a sensitive and reproducible technique for evaluating serial changes in ejection fraction and dV/dt in individual subjects over a wide range of ventricular function.

Acknowledgment

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Tricuspid Regurgitation in Tricuspid Valve Prolapse Demonstrated With Contrast Cross-Sectional Echocardiography

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To determine the prevalence of tricuspid regurgitation in patients with tricuspid valve prolapse and to define further the criteria for the diagnosis of tricuspid regurgitation on contrast echocardiography, evaluation was made of 45 patients who had adequate contrast studies. There were four groups of patients: Group A, 10 healthy control subjects with no evidence of structural heart disease on cardiac catheterization; group B, 10 patients with classic clinical evidence of tricuspid regurgitation; group C, 10 patients with cross-sectional echocardiographic evidence of mitral valve prolapse without tricuspid valve prolapse; and group D, 15 patients with both mitral and tricuspid valve prolapse on cross-sectional echocardiography.

Tricuspid regurgitation was sought in each group by using the subxiphoid echocardiographic approach with peripheral venous injection of saline solution. The diagnosis required the presence of microcavitations in both the inferior vena cava and hepatic veins for at least three consecutive cardiac cycles. Tricuspid regurgitation was observed in no patients in group A, 10 of 10 patients in group B, 0 of 10 in groups C and 6 of 15 (40 percent) in group D. Contrast cross-sectional echocardiography proved to be a reliable technique for identifying tricuspid regurgitation with a high degree of specificity and sensitivity. Patients with tricuspid valve prolapse had a 40 percent prevalence rate of tricuspid regurgitation. This finding may identify a subgroup that requires particularly careful clinical follow-up care.

A wide prevalence of tricuspid valve prolapse has been previously demonstrated in a selected symptomatic population with mitral valve prolapse.[1] The association of mitral regurgitation with mitral valve prolapse has been well defined,[2] whereas the prevalence of tricuspid regurgitation in patients with tricuspid valve prolapse has not been explored. Tricuspid regurgitation is difficult to diagnose because it may not be apparent on physical examination[3] and its angiographic definition is obscured because a catheter must be placed across the tricuspid valve to perform right ventricular angiography. In addition, the systolic murmur of low pressure tricuspid regurgitation may not be readily detected or may be masked by other systolic murmurs on physical examination.[3]

Recently, contrast cross-sectional echocardiography has been utilized to identify tricuspid regurgitation with a high degree of specificity and sensitivity.[4] We initiated this study to define this technique further and to determine the prevalence of tricuspid regurgitation in patients with tricuspid valve prolapse.

Methods

Control population: The control subjects constituted two groups. *Group A,* (normal group) comprised 10 clinically healthy subjects (5 women) with a mean age of 55 ± 15 years. All had normal findings on physical examination, electrocardiography, chest X-ray film and cardiac catheterization.

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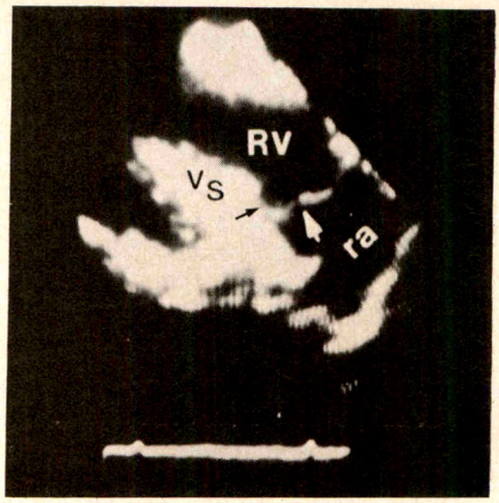


FIGURE 1. Systolic frame from a parasternal long axis view of the right ventricular inflow tract demonstrating the right atrium (ra), right ventricle (RV) and interventricular septum (VS). The **small black arrow** points to the level of the tricuspid valve anulus and thus identifies that the tricuspid valve leaflets, which (**white arrow**) lie prolapsed, are within the right atrium during systole.

Group B (positive control group) comprised 10 patients (7 women) with a mean age of 56 ± 16 years. All had clear evidence of tricuspid regurgitation. Five of these patients had mitral stenosis with pulmonary hypertension and had had tricuspid regurgitation defined on physical examination[3] and with angiographic techniques. Of the remaining five, three had idiopathic congestive cardiomyopathy with biventricular failure, one had Ebstein's anomaly and one had primary pulmonary hypertension with right heart failure. In these latter five patients tricuspid regurgitation had been diagnosed on the basis of classic physical findings.[3]

Study population: The study patients also constituted two groups. *Group C* comprised 10 patients (8 women) with a mean age of 33 ± 16 years. All had a cross-sectional echocardiographic diagnosis of only mitral valve prolapse by the criteria of Gilbert et al.[5] *Group D,* the experimental group, comprised 15 patients (9 women) with a mean age of 46 ± 22 years. All had cross-sectional echocardiographic evidence of both mitral valve prolapse and concomitant tricuspid valve prolapse. The diagnosis of tricuspid valve prolapse (Fig. 1) was defined by echocardiographic criteria.[1]

Cross-sectional echocardiographic studies: These were obtained using a wide angle 84° commercially available phased-array system (Varian V-3000) with a transducer containing 32 mounted piezo-electric crystals with a diameter of 1.3 by 1.2 inches (3.30 by 3.05 cm) at the skin level. Studies were recorded on videotape (Sanyo) and were later reviewed in real time, slow motion and frame by frame analysis. Individual frames selected for figures were photographed using a Polaroid® camera. The quality of these still frame images was significantly degraded because only one half of the line density was present during the still framing. M mode echocardiographic studies were obtained using a Smith-Kline Ekoline 20 A echocardiograph with a 2.25 megahertz transducer.

Contrast echocardiography: This procedure was performed by standard techniques which involved implanting a 19 or 21 gauge peripheral scalp vein needle into a forearm vein and rapidly injecting 10 cc of normal saline solution.[6] Standard short axis, right ventricular inflow or apical four

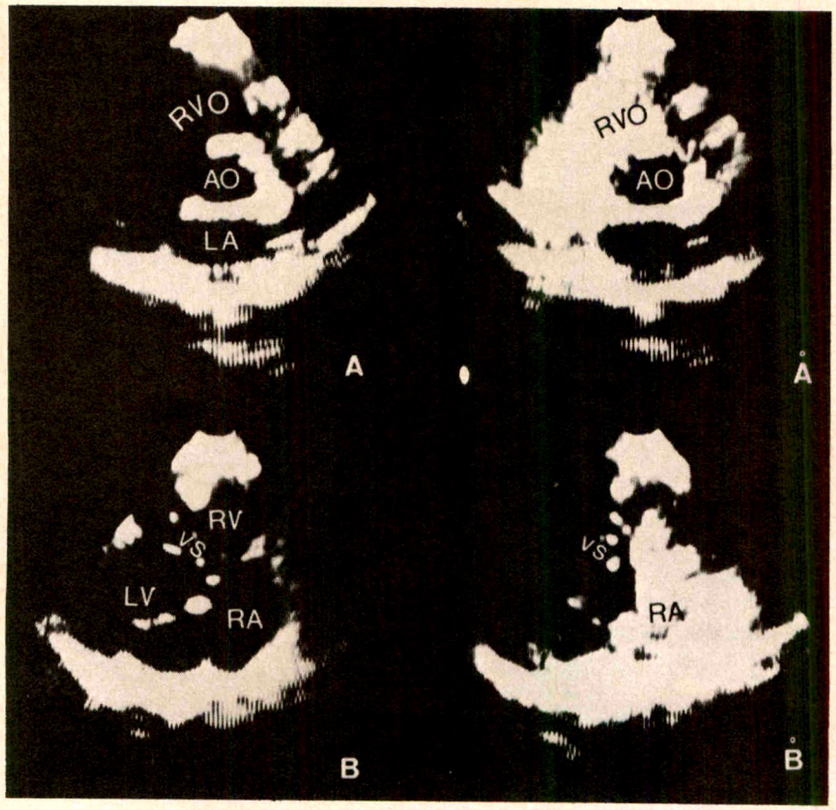


FIGURE 2. Left panels, cross-sectional echocardiographic views before the peripheral venous injection of saline solution. **A,** short axis view at the base of the heart demonstrating the right ventricular outflow tract (RVO), aorta (AO) and left atrium (LA). **B,** right ventricular longitudinal inflow tract view depicting the right ventricle (RV), interventricular septum (VS), right atrium (RA), and left ventricle (LV). **Right panels,** after injection, microcavitations are seen in the right atrium and right ventricle.

chamber echocardiographic views,[7] or all three, were visualized at the time of the saline bolus injection. To qualify for this study, microcavitations had to be seen in both the right atrium and the right ventricle (Fig. 2). Contrast cross-sectional echocardiography was attempted in 54 patients; 9 of these were excluded because microcavitation was inadequately visualized. Four of the nine had mitral and tricuspid valve prolapse, two had mitral valve prolapse alone, and the remaining three were normal control subjects. Once a patient qualified for inclusion in the study, the transducer was placed 1 to 2 cm to the right of the mid line of the subxiphoid area, and a short axis view of the inferior vena cava and hepatic vein or veins[7] was obtained (Fig. 3). The right atrium and in some cases a portion of the right ventricle could be seen in this view. An additional 10 cc of saline solution was injected with continuous videotape recording of the subxiphoid view. Tricuspid regurgitation was defined if microcavitations were identified in not only the inferior vena cava but also in one or more hepatic veins for at least three cardiac cycles. The inferior vena cava and hepatic veins were visualized with careful transducer angulation to avoid superimposition of the right atrium over the inferior vena cava; the latter may falsely suggest the presence of microcavitations in the inferior vena cava when they are present only in the right atrium.

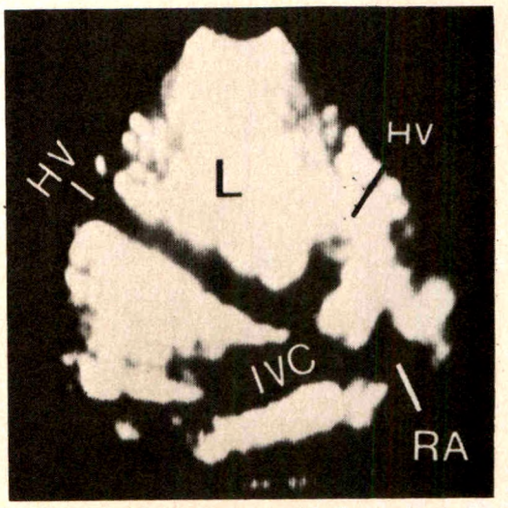


FIGURE 3. Subxiphoid view demonstrating the short axis view of the liver (L), hepatic veins (HV), inferior vena cava (IVC) and a part of the right atrium (RA).

Results

Group A (normal subjects): Contrast echocardiographic studies were adequately obtained in all 10 subjects with opacification of the right heart chambers during the initial study. In all 10, injection of saline solution showed no microcavitations in the inferior vena cava or hepatic veins in the subxiphoid view.

Group B (patients with tricuspid regurgitation): All 10 patients with clinical or angiographic evidence, or both, of tricuspid regurgitation had microcavitations seen in both the inferior vena cava and hepatic veins for at least three cardiac cycles (Fig. 4).

Group C (patients with mitral valve prolapse without tricuspid valve prolapse): None of the 10 patients with mitral valve prolapse without tricuspid valve prolapse by cross-sectional echocardiographic criteria demonstrated evidence of microcavitation in the hepatic veins or inferior vena cava.

Group D (patients with mitral and tricuspid valve prolapse): Six (40 percent) of the 15 patients with cross-sectional echocardiographic evidence of both mitral and tricuspid valve prolapse demonstrated tricuspid regurgitation on contrast echocardiography (Fig. 5). In these six patients the subxiphoid view revealed microcavitations in the inferior vena cava and one or more hepatic veins for at least three cardiac cycles after injection of saline solution. In three patients tricuspid valve prolapse was judged as mild and in three as moderate in severity. Of the nine patients with tricuspid valve prolapse without tricuspid regurgitation, four had mild, four moderate and one severe tricuspid valve prolapse.

Table I summarizes the clinical findings in these four groups.

Discussion

Tricuspid regurgitation defined with contrast echocardiography: Our study revealed a 40 percent prevalence rate of tricuspid regurgitation in patients with tricuspid valve prolapse studied with contrast cross-sectional echocardiography. Contrast cross-sec-

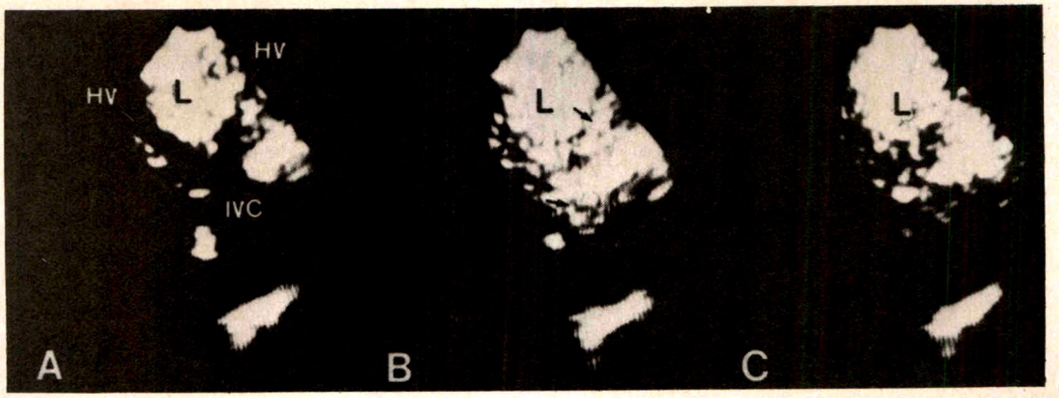


FIGURE 4. Patient with mitral stenosis and pulmonary arterial hypertension (group B). **A**, subxiphoid view of the inferior vena cava (IVC), hepatic veins (HV), and liver (L). **B** and **C** were taken after peripheral venous saline injection. **B**, the **black arrow** points out microcavitations in the hepatic vein which persisted for over 30 seconds as shown in **C**. The inferior vena cava is dilated as compared to Figure 3.

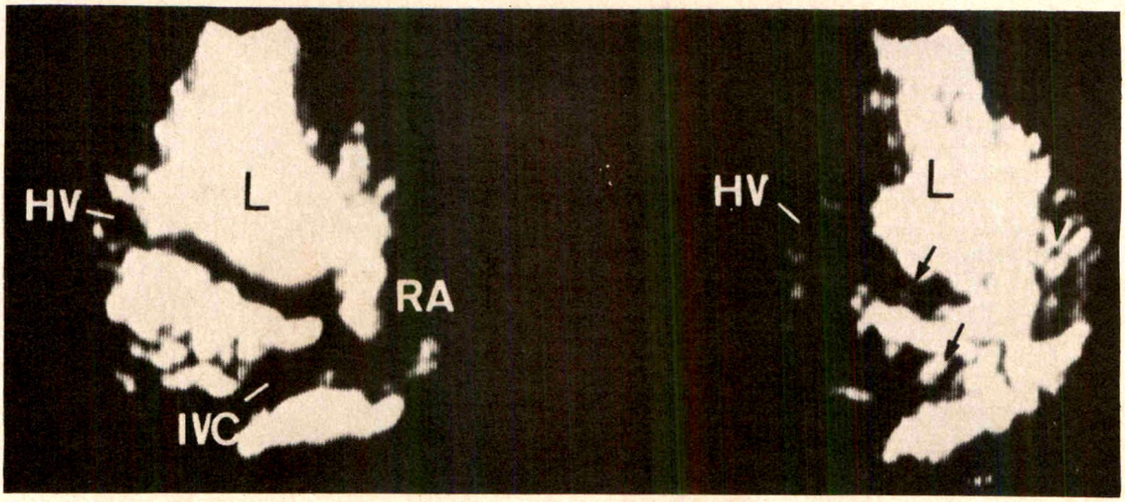


FIGURE 5. Patient with tricuspid valve prolapse and tricuspid regurgitation (group D). **Left,** short axis subxiphoid view of the hepatic vein (HV), inferior vena cava (IVC), liver (L) and right atrium (RA) taken *before* peripheral venous injection of saline solution. **Right,** microcavitations are present in the inferior vena cava and hepatic vein (seen at and to the right of the **black arrows**), documenting the presence of tricuspid regurgitation.

tional echocardiography detected the presence of tricuspid regurgitation with a high degree of sensitivity and specificity when the criteria of Lieppe et al.[4] were used. These criteria require the presence of to and fro motion of microcavitations across the tricuspid valve or in the inferior vena cava. In the study of Lieppe et al.,[4] all patients with clinically diagnosed tricuspid regurgitation had tricuspid regurgitation defined on contrast echocardiography, whereas no patient in the normal control group had this echocardiographic finding. The technique used in that study (in the subxiphoid view) may yield a false positive result because the right atrium may be superimposed on the inferior vena cava as a result of abnormal angulation of the transducer. Thus, microcavitations may appear to be present in the inferior vena cava when in fact they are isolated to the right atrium. Our more stringent criteria for the definition of tricuspid regurgitation required microcavitations to be present in both the inferior vena cava and the hepatic veins, with a to and fro motion for at least three cardiac cycles.

There was no clear correlation between the degree of persistence or intensity of microcavitation in the inferior vena cava in our patients with severe tricuspid regurgitation (group B) and that in patients with tricuspid valve prolapse (group D), who had no evidence of tricuspid regurgitation on clinical examination. The inferior vena cava and right atrium were enlarged in all subjects in group B but in none of those in group D. In addition, there was no correlation between the degree of tricuspid valve prolapse with the presence of tricuspid regurgitation.

Prevalence of tricuspid regurgitation in tricuspid valve prolapse: The 40 percent prevalence rate of tricuspid regurgitation in tricuspid valve prolapse documented in our study is similar to the high prevalence rates (50 to 65 percent) of systolic murmurs or angiographically proved mitral regurgitation in the

TABLE I

Clinical Findings in the Control and Study Groups

Group	n	Mean Age (yr)	Sex (% female)	Systolic Sound		Cardiac Symptoms	TR by Contrast Echo
				Click	Murmur*		
A: Normal control	10	55 ± 15	50	0/10	0/10	3/10 (chest pain)	0/10
B: Positive control (tricuspid regurgitation)	10	56 ± 16	70	0/10	10/10	10/10	10/10
C: Mitral valve prolapse without tricuspid valve prolapse	10	33 ± 16	80	4/10	6/10	4/10 (chest pain and/or palpitations)	0/10
D: Mitral valve prolapse with tricuspid valve prolapse	15	46 ± 33	60	10/15	13/15	11/15 (chest pain and/or palpitations)	6/15

* By physical examination.
Echo = cross-sectional echocardiography; TR = tricuspid regurgitation.

mitral valve prolapse syndrome.[2,8] Unfortunately, minor degrees of tricuspid regurgitation, which would be expected in an unselected population of patients with tricuspid valve prolapse, are extremely difficult to diagnose because hemodynamic and angiographic studies are limited by the requirement that a catheter cross the tricuspid valve.[4] Physical findings of a systolic murmur and abnormal jugular venous pressure contour are usually present and diagnostic in patients with moderately severe or severe high pressure tricuspid regurgitation. However, they are often absent in patients with minimal or low pressure tricuspid regurgitation, in whom the murmur is usually not holosystolic but nonspecific in character.[3] In such patients, cross-sectional echocardiography with contrast enhancement appears to provide a sensitive and specific means of diagnosing tricuspid regurgitation. This technique is usually easy to perform because the abdomen is air-free and images are usually of high quality. The finding of a 40 percent prevalence rate of tricuspid regurgitation in patients with tricuspid valve prolapse suggests that this echocardiographic diagnosis is identifying an abnormal tricuspid valve that may be part of a more extensive spectrum of cardiac skeletal disease. It may also identify a subgroup of patients requiring particularly careful follow-up care.

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Body Surface Distribution of Exercise-Induced QRS Changes in Normal Subjects

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Previously reported clinical studies have suggested an important diagnostic role for exercise-induced QRS changes. To explore the spatial features of such alterations, anterior thoracic isopotential distributions were examined at rest and at 85 percent of maximal heart rate in 30 normal male volunteers. Results demonstrated that exercise caused a reduction in positive forces and an augmentation of negative voltages at most anterior thoracic sites. However, the locations of map extrema were not significantly altered. Difference maps, computed by subtracting time-aligned distributions at rest and during exercise, suggested that exercise generated an electrical field characterized by a central anterior minimum bordered superiorly by positive potentials. The minimum reached a peak magnitude in the middle portion of the QRS pattern, then declined in intensity. Although difference patterns during inscription of the QRS complex were similar to those computed during the P-R and S-T segments, time-intensity curves were discontinuous with marked and abrupt early increases and late decreases in strength in the QRS complex. These results suggest that two commonly considered mechanisms (effects of changes in intracavitary blood mass and of atrial repolarization) cannot be solely responsible for the observed effects.

All phases of the electrocardiogram are subject to exercise-induced alterations. Although S-T segment shifts are most commonly evaluated, variations in the P wave and P-R segment[1–3] and in the QRS complex[2–12] have clearly been documented. This report focuses on changes affecting the QRS complex in normal subjects during strenuous activity. Barrow and Ouer[4] considered such alterations to be those most commonly observed, occurring in 81 percent of normal men evaluated. More recently, Bonoris et al.[8,9] concluded that a reduction in R wave amplitude during exercise was a characteristic and, indeed, a diagnostic feature of normality, whereas an augmentation of this wave was highly suggestive of ventricular dysfunction. In contrast, Battler et al.[10] reported that R wave variations were poor correlates of exercise-induced changes in ventricular volume or ejection fraction. Thus, alterations in ventricular activation are of clinical importance.

This topic will be approached using the technique of isopotential body surface mapping. This procedure has successfully been applied to the study of S-T segment shifts during exercise in normal subjects[13] and in patients with ischemic heart disease,[14,15] portraying the distribution of cardiac potentials over large areas of the thoracic torso. In an analogous manner, the spatial distribution *and* magnitude of QRS complex aberrations may be described.

Methods

Study group: Thirty normal male volunteers, aged 21 to 27 years, were studied. All were free of circulatory disease, as determined by history, physical examination, routine electrocardiography and chest roentgenography. Voluntary informed consent was granted before study.

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Electrode system: Fourteen strips of six silver-silver chloride electrodes were placed on the anterior chest of each subject. This 84 electrode grid covered the torso surface from the right to the left posterior axillary lines and from the level of the clavicles to the inferior rib margins. Additional electrodes were placed proximally on the limbs[16] to record standard and unipolar limb leads and to derive the Wilson central terminal voltage. Details of electrode construction have been reported.[13] Electrodes were restricted to the anterior chest to (1) reduce patient discomfort and noise levels (both would have been greater if the subjects were lying on posterior electrodes), and (2) reduce the amount of hardware needed to record from more than 84 electrodes simultaneously during exercise.

Exercise protocol: Exercise stress tests were performed using a supine bicycle ergometer protocol. All subjects initiated exercise at a load of 300 kg-m/min. The load was then increased without interruption of exercise by 100 to 150 kg-m/min at 2 minute intervals until 85 percent of maximal predicted heart rate was reached and maintained for 2 minutes.[17]

A supine bicycle ergometer protocol was selected to (1) reduce noise levels beyond those achievable with motor-driven treadmill devices, and (2) to enhance electrode stability and thus reduce baseline drift by the thoracic fixation afforded by the recumbant posture.

Data acquisition system: Voltages sensed by torso electrodes were amplified by a bank of 84 differential (electrode potential versus Wilson central terminal voltage) capacitor coupled amplifiers. Gains were set at 1,000 or 2,000, and the time constant fixed at 2 seconds. Additional amplifiers were used to multiply limb electrode output.

Amplified potentials were digitized on-line at a sampling rate of 500 samples/channel per second, and digital data were stored on magnetic tape for later off-line processing. Data were collected simultaneously from all electrodes for 15 second periods before, at 2 minute intervals during, and at 2 minute intervals after completion of the test protocol. The 15 second segments during exercise corresponded to the final quarter-minute of work at a given load. Exercise was not interrupted for data sampling.

All electrocardiographic channels were examined before exercise to ensure (1) normality of the QRS-T complex, (2) stability of baseline, and (3) noise-free recordings. One channel, recorded from an electrode approximating a V_5 location, was selected for continuous monitoring.

Data analysis: Cycle averaging routines have been described in detail in prior reports from this laboratory.[13,18] In essence, all cycles determined to have morphologically similar P-QRS-T patterns by an automated autocorrelation routine were averaged to reduce random noise. Onsets and offsets of the electrocardiographic waves (P wave, QRS complex and T wave) were then manually determined from a high gain, time-expanded plot of root-mean-square potential. A 10 to 20 ms portion of the terminal T-P segment was averaged and used as a baseline reference because (1) it represents the least active phase of the cardiac cycle,[19] and (2) its selection permitted evaluation of the P-R segment potentials, which would not have been possible had the P-R segment itself been utilized as a reference.

The QRS interval of each lead before and during exercise was subdivided into 49 segments of equal duration. A 5 point cubic routine was utilized to interpolate the 50 data points. This time normalization facilitated comparison and subtraction of patterns sensed at equivalent moments during cardiac excitation before and during exercise. Data distortion was minimal as evidenced by the QRS duration, which was insignificantly changed with exercise (see later). Similar time normalization schemata have been utilized by Blomqvist[2] and by Simoons and Hugenholtz.[3]

Isopotential maps were constructed using a combined linear-bilinear interpolation routine. Contour lines were drawn at predetermined intervals (0 and ± 10, 20, 40, 60, 100, 150, 250, 400, 600, 1,000 (and so forth) μV). Maps were displayed at 2 ms intervals during the P-R and ST-T intervals and at each of the 50 time-normalized points during the QRS complex. Timing of each map was expressed as the number of milliseconds of the instant under consideration from the onset or offset of the QRS complex for points in the P-R or S-T segment or as the percent of elapsed time during inscription of the QRS complex.

A paired t test was used to determine the significance of exercise-induced alterations, and a significance level of $p = 0.01$ was relied on to evaluate statistical significance. All data are presented as mean ± 1 standard deviation.

Results

Exercise responses: In each subject the predicted submaximal heart rate was reached and maintained for 2 minutes. Mean resting and peak heart rate was 68.8 ± 12.1 and 164.2 ± 9.4 beats/min, respectively. The mean QRS duration was 78.4 ± 2.4 ms at rest and 77.1 ± 2.8 ms during exercise. Differences between measurements at rest and during exercise ranged from +4 to −4 ms (−0.6 ± 0.8 ms) and were not statistically significant ($p > 0.1$) using a paired t test.

Examples of averaged QRS-T waveforms recorded from one vertically oriented strip of six electrodes crossing the V_5 precordial site are presented in Figure 1. Waveforms in the left column were sensed at rest (heart rate 68 beats/min); those in the right column were recorded during exercise (heart rate 164 beats/min). Note (1) the low noise levels of recordings during exercise, and (2) the general reduction in amplitude without a major change in QRS configuration during exercise.

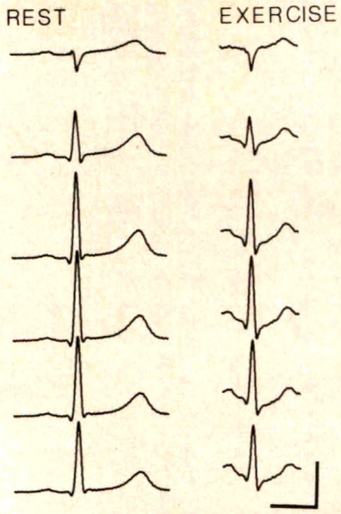


FIGURE 1. Electrocardiographic waveforms recorded from six anterior precordial electrodes at rest (**left column**) and during supine exercise (**right column**). The six electrodes were located on a vertical line extending through the V_5 precordial electrode position. The scale figure (**lower right**) corresponds to 200 ms horizontally and 1 mV vertically.

Isopotential distributions at rest and during exercise: Because all subjects demonstrated qualitatively similar results, data from one representative study will be offered. Anterior thoracic body surface isopotential maps will be presented in a standard format. Positions of the 84 electrodes are indicated by plus or minus signs, corresponding to the polarity of the voltage registered at that site. The location of the sternal notch is marked by a V and the positions of the six standard precordial electrode sites are denoted by solid squares. Thus, the center of each map corresponds to the mid sternal line and the lateral borders to the two posterior axillary lines. Points of equal potential are connected by solid contour lines; zero level isopotential lines are overdrawn for emphasis.

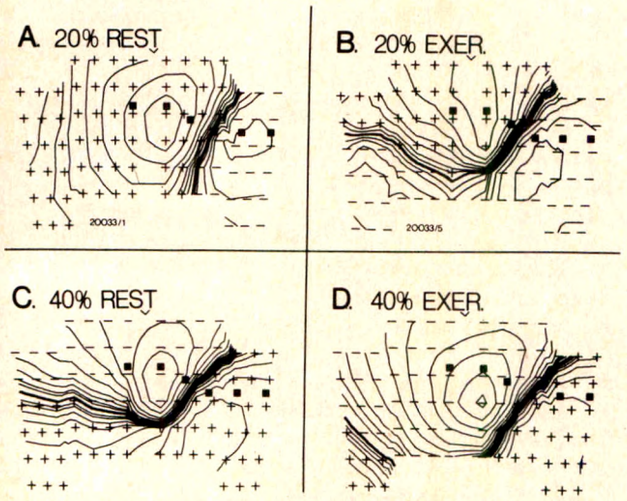


FIGURE 2. Anterior thoracic isopotential distributions, constructed as detailed in the text, from potentials sensed before and during exercise at instants 20 and 40 percent through the time-normalized QRS complex. **A**, 20 percent instant, at rest. **B**, 20 percent instant, at peak exercise. **C**, 40 percent instant, at rest. **D**, 40 percent instant, at peak exercise. Magnitudes of the extrema are given in the text.

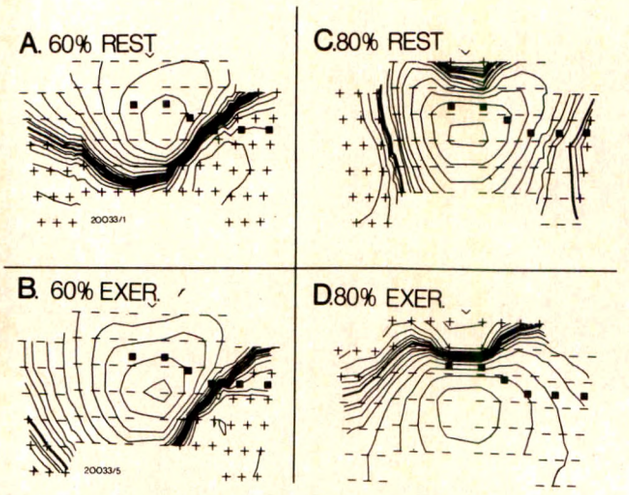


FIGURE 3. Isopotential distributions, drawn as in Figure 1, from potentials registered at 60 percent through the QRS complex at rest (**A**) and at peak exercise (**B**), and 80 percent through the QRS at rest (**C**) and during exercise (**D**). Magnitudes of extrema are detailed in the text.

Examples of isopotential distributions before exercise and at peak heart rate are presented in Figures 2 and 3. With 20 percent of the QRS complex inscribed, the isopotential pattern at rest was characterized by a central maximum, or zone of peak positive potential, and a left lateral area of peak negative voltage or minimum (Fig. 2A). The maximal positive and negative potential was 585 and −112 μV, respectively. During exercise, at a heart rate of 164 beats/min, the distribution at the same point in the normalized QRS complex (Fig. 2B) was similarly dominated by an anterior maximum and a lateral minimum. However, negative potentials were more widespread on the inferior and right thoracic surfaces. Additionally, the peak positive potential was reduced to 315 μV whereas peak negative voltage decreased to −288 μV. Positions of the electrodes sensing maximal and minimal voltages did not vary.

Patterns at rest (Fig. 2C) and during exercise (Fig. 2D) with 40 percent of the QRS complex inscribed were dominated by an anterior minimum surrounded by positive potentials on the inferior and lateral margins. The two distributions again differed in that (1) the extent of the negative potentials increased inferiorly, (2) the magnitude of peak positive potentials decreased from 1,237 to 932 μV, and (3) the magnitude of peak negative voltages increased from −2,449 to −4,577 μV. The locations of maximums and minimums did not vary.

Patterns at rest and during exercise with 60 percent of the QRS complex inscribed (Fig. 3, A and B) were similar to those previously described. Peak positive and negative voltages changed from 1,895 to 1,017 μV and from −3653 to −4840 μV, respectively, without changes in locations of extrema.

With 80 percent of the QRS complex passed, a new superior maximum emerged (Fig. 3C). Exercise once again extended and intensified (−112 versus −1,481 μV) the negative forces, but the strength of the superior maximum increased from 110 to 450 μV after exercise (Fig. 3D).

To highlight the differences between patterns at rest and during exercise, preexercise distributions were subtracted from the peak exercise patterns sensed at the corresponding point of the time-normalized QRS complex. Thus, for example, the distribution presented in Figure 4A was computed by subtracting the voltages depicted in Figure 2A from those of Figure 2B. These "difference maps" depicted the spatial distribution of the changes induced by exercise. (In this study, the baseline pattern was subtracted from the intervention distribution (that is, the opposite sequence from that previously described by McLaughlin et al.[20]) At each time point discussed earlier, the effect of exercise was to generate a field characterized by negative potentials over much of the anterior thorax but bordered superiorly by positive potentials (Fig. 4). The strength of the

minimum increased to the middle of the QRS complex, and then declined, being −270, −2,461, −1,929 and −689 μV at points 20, 40, 60 and 80 percent into the QRS complex, respectively. The intensity of the positive rim likewise increased, being 117 μV at 20 percent and 539 μV at 60 percent instants. In addition, this positive area increased in extent in the latter half of the QRS complex.

Another method of evaluating the relation between patterns at rest and during exercise was to calculate correlation coefficients comparing the two distributions at each 2 percent interval. Coefficients were computed as described by Horan and Flowers[21] using the formula

$$r = \frac{\sum X_i Y_i}{\sqrt{\sum X_i^2 \sum Y_i^2}},$$

where r = correlation coefficient, X_i = potential at each of the 84 electrodes at rest, and Y_i = potential at the site during exertion. Correlation coefficients ranged from 0.55 to 0.89, with peak values in the middle segment of the QRS complex. Values at all instants were statistically significant. Thus, although exercise did alter the magnitudes of surface potentials, the overall patterns remained significantly similar.

Peak R and S wave distributions: The maximal positive and negative potentials in the 50 QRS maps of each subject, at rest and during exercise, were determined. These values corresponded to the height of the tallest R wave and the depth of the deepest S wave recordable at any anterior chest locus. The locations of these peak voltages were likewise determined and tabulated.

The maximal R wave amplitude was 2,031.1 ± 405.1 μV at rest and 1,694.4 ± 464.1 μV on exercise. The difference between the values varied from −8.9 to −177.8 μV (−336.7 ± 229.9) and was statistically significant. In all cases, peak R wave amplitude decreased with exercise but in no case did the locus of the peak shift by more than one electrode row or column.

The mean depth of the S wave, in contrast, increased by 462.7 ± 536.46 μV after exercise ($p < 0.01$), decreasing in only three cases. Thus, in most cases studied, exercise caused a decrease (less positive or more negative) in peak R and S wave amplitudes.

To portray the spatial distribution of these changes, R wave and S wave amplitudes, peak R and S wave magnitudes and the amplitude of the entire QRS complex at each of the 84 electrode sites were calculated. Values before and after exercise were subtracted, and the differences plotted as isopotential maps (Fig. 5). R waves, S waves or QRS complexes recorded from electrodes lying in segments of such maps with negative polarities were reduced (less positive R or more negative S waves, or lower total QRS amplitude) in magnitude with exercise. Those sensed from zones with positive voltages demonstrated opposite directional changes. R wave amplitudes registered from electrode sites on most of the anterior thorax were reduced in magnitude (Fig. 5A). The greatest reductions were observed near V_3 and V_4 electrode sites. In contrast, electrodes along the su-

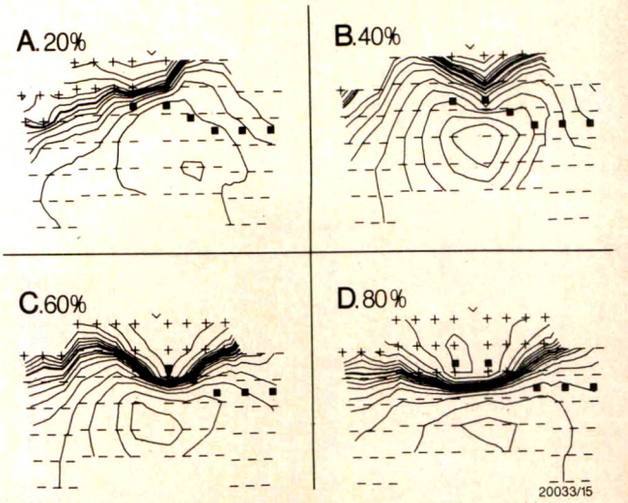


FIGURE 4. Isopotential difference maps, depicting the difference in potentials registered at a given instant before and during exercise. Conventions as in prior illustrations. **A**, differences in potentials sensed 20 percent through the QRS complex, computed by subtracting voltages in Figure **2A** from those in Figure **2B. B,** difference between **C** and **D** of Figure **2**, corresponding to voltages sensed 40 percent through the QRS complex. **C**, difference between **A** and **B** of Figure 3. **D**, difference map computed by subtracting **C** and **D** of Figure 3.

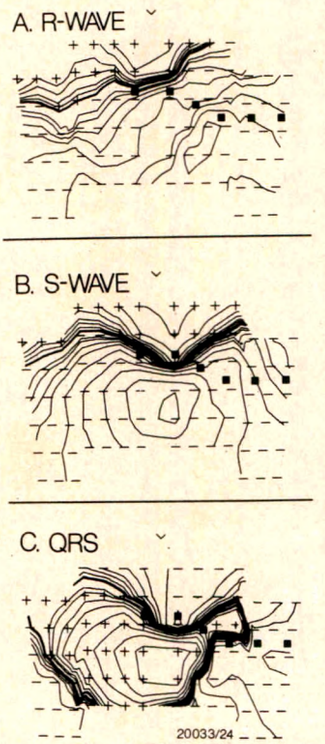


FIGURE 5. A, isopotential distribution depicting the change in the maximal amplitude of the R wave registered by each torso electrode during exercise. R waves sensed from electrodes with positive values in the map increased in magnitude whereas those with negative signs decreased in amplitude. **B**, spatial distribution of changes in S wave depth, computed as in **A**. Negative values indicate increasing negativity or increasing S wave depth with exercise. **C**, distribution of changes in overall QRS amplitude (R wave height plus S wave depth) during exercise, calculated as before.

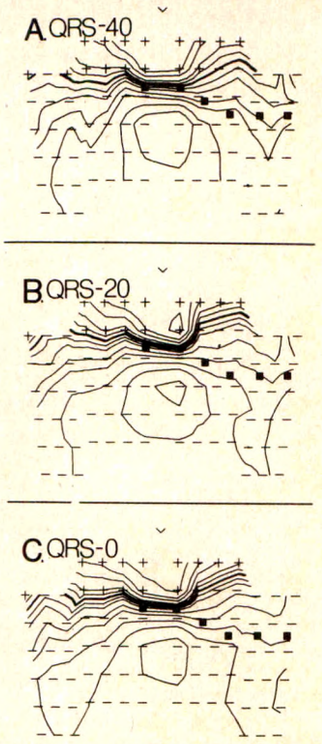


FIGURE 6. Difference maps, computed as in Figure 4, depicting the effects of exercise on potentials sensed 40 ms (**A**) and 20 ms (**B**) before and at (**C**) the onset of the QRS complex. Maximal negative potentials are −244 μV (**A**), −294 μV (**B**) and −323 μV (**C**). Peak positive potentials in A, B and C are 98, 119 and 133 μV, respectively.

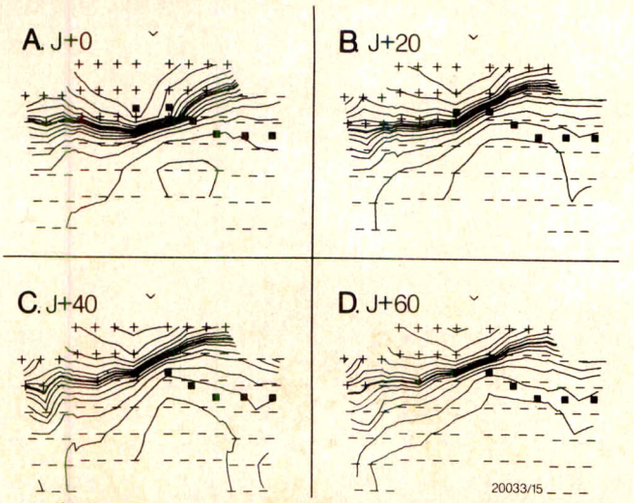


FIGURE 7. Difference maps, as in Figures 4 and 6, calculated from potentials recorded at the onset of the S-T segment (J point) (**A**) and at instants 20 ms (**B**), 40 ms (**C**) and 60 ms (**D**) into the ST-T interval. Peak positive and negative voltages measured 236 and −453 μV (**A**), 212 and −389 μV (**B**), 169 and − 320 μV (**C**) and 160 and −238 μV (**D**), respectively.

perior border of the chest sensed increased R wave amplitudes during exercise. S waves deepened during exercise over much of the torso (Fig. 5B), with less negative forces being sensed only over the superior torso. The net effect on overall QRS amplitude was more complex (Fig. 5C), with increased amplitude recorded from sites on the central and right areas of the torso and lowered amplitudes from sites on the superior and left. These data thus indicated that the changes in the R and S waves and QRS amplitude caused by exercise were regional in nature and, hence, were lead-dependent.

Amplitudes of the R and S waves in the 12 standard electrocardiographic leads were similarly calculated. The R wave amplitude did not change significantly in lead aVL, increased in lead aVR and decreased significantly in all other leads. The greatest reduction was in the V_4 R wave, which decreased by 489.9 ± 298.9 μV. The S wave depth decreased in lead aVR, did not vary in leads aVL, V_1 and V_2, and increased in the remaining eight leads. Here, too, the greatest change was in V_4 records, with the S wave depth increasing by 466.6 ± 174.6 μV. Thus, lead dependency was similarly observed standard electrocardiographic lead configurations.

Relation to R-R and S-T segment responses: The QRS difference map patterns, such as those portrayed in Figure 4, were compared with those computed at 2 ms intervals during the terminal 40 ms of the P-R segment and the initial 80 ms of the S-T segment. The difference maps presented in Figure 6 were drawn from data sensed 40 ms (panel A) and 20 ms (panel B) before and at (panel C) the manually determined onset of the QRS complex. At each instant, exercise induced a field characterized by a central minimum with negative potentials over most of the torso, and positive voltages restricted to superior segments of the chest. Peak negative and positive voltages increased toward the end of the P-R segment. Patterns in Figure 7 correspond to the differences in voltages at rest and during exercise registered at the J point (panel A) and at instants of 20 ms (panel B), 40 ms (panel C) and 60 ms (panel D) into the S-T segment. Here, too, the distributions are characterized by anterior negativity and superior positivity.

Difference distributions computed during the P-R segment, QRS complex and S-T interval were compared as to location and intensity of extrema. In any one subject, the location of the electrode sensing the greatest positive or negative voltage did not shift by more than one electrode row or column, or both, at all studied instants during the three electrocardiographic periods. The intensities of the minimums in the difference maps are plotted in Figure 8, which shows in panel A the superposed results of all subjects and the means and standard deviations in panel B. This figure shows that the magnitudes varied widely among subjects, and that the intensities of the minimum increased abruptly soon after the onset of the QRS complex, reaching a peak near the middle of ventricular activation. Thus, whereas the spatial location of the exercise-induced effect was similar during atrial and ventricular recovery and during ventricular excitation, the intensities were disparate.

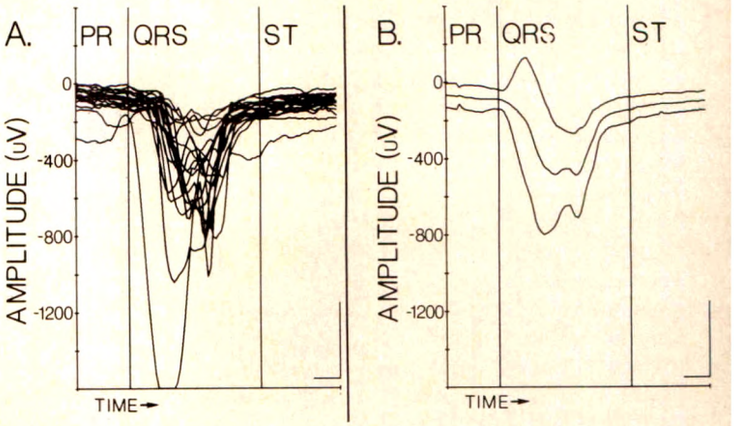


FIGURE 8. Time course of changes in the intensity of the exercise-induced minimum depicted in Figures 4, 5 and 6. The time interval examined begins 40 ms before the onset of (**left margin**) and ends 80 ms after the offset of (**right margin**) the QRS complex. **A**, data from each subject are superposed on one another. **B**, mean (**center line**) and ± 1 standard deviation limits (**upper and lower contours,** respectively) of the magnitudes are plotted. Scale figures correspond to 400 μV vertically and 20 ms (P-R segment and S-T segment) or 20 percent (QRS interval) horizontally. **Vertical lines** delimit the onset and offset of the QRS complex.

Discussion

Our results have shown in detail the spatial distribution of exercise-induced effects during inscription of the QRS complex and during portions of the P-R and S-T segments. Significant findings included (1) the reduction in peak positive potential at most but not all instants in the QRS complex without a shift in extrema location, (2) the increase in peak negative potential at all time points in most subjects, (3) the location-dependent nature of the R and S wave and QRS complex amplitude changes, and (4) the continuity of QRS changes spatially but not in magnitude with those detected during other portions of the cardiac cycle.

Supine versus upright exercise: The rationale for using a supine rather than an upright exercise protocol was given earlier. Differences in the physiologic response to exertion in the two positions have been studied by several investigators. Epstein et al.[22] concluded that, in normal subjects, the relation between heart rate and oxygen consumption was the same during supine bicycle and upright treadmill exercise. Bevegard et al.[23] reported similar heart rate responses to supine and sitting leg exertion in normal subjects, although stroke volume increased more in the supine position. Similar data were reported by McGregor et al.[24] Thus, the current use of supine exercise protocols to study normal electrical and hemodynamic[25–27] responses to exercise provides at least as great a circulatory stress as does the use of upright exertion.

Reported exercise-induced R wave changes in normal subjects: Numerous electrocardiographic studies have reported the prevalence of R wave changes in normal subjects. Barrow and Ouer,[4] in 1943, detected QRS changes in 81 percent of 100 normal subjects; the QRS voltage decreased in 49 and increased in 32 persons. Lloyd-Thomas[6] reported a reduction in R wave amplitude in 55 of 67 subjects, with increases in magnitude occurring in the remaining 12. Kentala et al.[7] described augmentation of R wave magnitude early during exercise, followed by reduction in amplitude after completion of strenuous exercise. Other recent studies[8–12] have reported a reduction in R wave amplitude in 51 to 97 percent of subjects without ischemic heart disease.

In contrast, vectorcardiographic evaluations have not noted such changes. Kahn and Simonson[5] reported that exercise caused a rightward shift in the QRS axis and shifted the mean QRS forces superiorly and to the right; terminal forces deviated upward, rightward and anteriorly. Magnitudes were not assessed. Simoons and Hugenholtz[3] noted similar instantaneous vectoral changes but noted no significant alteration in magnitude or orientation of maximal QRS vectors.

Possible causes for the differing results include differences in patient selection variables, exercise protocol formats[10] and electrocardiographic lead system selection. Our data relate only to the last consideration. The importance of lead selection has been documented.[10,11] In one study,[11] R wave amplitude was reduced in 38 of 39 normal subjects in lead CM_5 but in only 34 in lead V_5. Similarly, significant reductions in R wave height were noted[10] in lead V_5 and the Frank X lead, but not in the Y and Z leads.

Role of electrocardiographic lead sensitivity versus QRS vector orientations: The isopotential difference maps presented in Figures 4 and 5 suggest a basis for this lead sensitivity. Over different areas of the chest, both instantaneous and maximal R wave amplitudes may decrease or increase. Thus, one lead system may sense an increase in R wave amplitude (for example, lead aVR) because of its lead vector, whereas most other leads (the standard precordial leads) would record reduced R wave magnitudes. Of specific interest is the difference between leads V_5 and CM_5 noted by Wolthuis et al.[11] The negative terminal of CM_5 lying over the sternal notch would sense positive R wave differences whereas its opposite terminal at the V_5 electrode site falls in a zone of negative potential difference. A bipolar recording would thus register greater negative forces than the standard V_5 lead, whose negative terminal is at a theoretical zero level.

Data referred to earlier suggest a second concept. Vectorcardiographic studies have suggested that QRS vector orientation may change during exercise without a variation in vector magnitude.[3,5] The differing relation

between a given electrocardiographic lead and the heart vector could then cause a change in voltage sensed by that lead even though source strength did not vary. If so, isopotential distributions would be expected to show a shift in location without major alteration in magnitude of the extrema. However, patterns in Figure 4 illustrate the opposite (that is, major changes in magnitude without significant translocations). Thus, current results do not support the hypothesis that R wave differences as recorded in electrocardiographic leads are due primarily to reorientation of cardiac forces.

Role of exercise-induced change in activation sequence: It must be recognized that the lack of change in position of extrema does not necessarily imply a constancy of the source. Two aspects of this problem may be considered. First, it is clear from experimental work that changes in the characteristics of the cardiac source are not uniformly accompanied by parallel changes in the surface electrocardiogram.[18] Thus, the same surface effect observed at two instants may be due to two different cardiac events. Second, the use of time-normalization routines must be shown not to cause significant temporal displacement of signals, particularly if subtraction methods are used. In the current study, the mean change in QRS duration was not statistically significant and, indeed, was less than one sampling interval of 2 ms. However, in the absence of specific knowledge of waveform timing, little can be said about possible exercise-induced alterations in activation sequence.

Role of exercise-induced changes in intracavitary blood mass: The most commonly suggested mechanism for the R wave variations under consideration is the effect of exercise-induced changes in the intracavitary blood pool. As formulated by Brody[28] and other investigators[29,30] and experimentally validated,[31,32] the presence of an intracavitary blood mass with a conductivity greater than that of the cardiac source will (1) increase the potentials generated by a dipole oriented radial to the hyperconductive tissue, (2) decrease the forces generated by tangentially oriented sources, and (3) enhance the dipolar character of the equivalent generator. The degree of augmentation or reduction is dependent on the location of the sensing electrode in relation to the source, is directly proportional to the size of the hyperconductive zone and to its conductivity, and is inversely proportional to the distance from the electrical source to the region of low resistivity.

Application of these principles to exercise electrocardiography is critically dependent on two concepts. First, directional changes in cardiac volumes or blood resistivity, or both, must be known. A reduction in heart size, and hence in the volume of hyperconductive fluid, has generally been assumed to occur during exercise.[8,9] Second, orientation of cardiac activation fronts must be considered. On the basis of data from human studies,[33,34] it has been considered that, during the early and middle portions of the QRS complex, activation fronts proceed in a direction radial to the intracavitary blood mass. However, late QRS depolarization of the basal segments of the ventricles proceeds with a tangential orientation. Thus, R waves in standard electrocardiographic leads would be expected to decrease in amplitude during exercise, because they are generated by forces directed radial to a hyperconductive mass of reduced size.

Two features of the isopotential distributions reported here are consistent with this interpretation. First, positive surface potentials over much of the anterior thorax were reduced in magnitude (Fig. 2 and 3). Thus, difference potentials were negative in polarity (Fig. 4). Second, positive forces appearing late in the QRS complex at sites on the superior precordium were augmented by exertion. As these potentials presumably derive from basal tangential activation fronts, this response would be anticipated.

Aspects of the current data are also inconsistent with a sole role of the intracavitary blood mass. The S wave depth increased during exercise (Fig. 2), rather than decreasing in absolute value as did R wave amplitude. Clearly, the role of hyperconductive tissues would be expected to have identical directional effects on forces of either polarity. This has been documented in the model studies previously reported.[31,32] Thus, experimental considerations also suggest that the effects of exercise on the intracavitary blood mass are not the only (and may not be a major) factor in the genesis of QRS changes during exercise.

Other reasons to question the role of this mechanism are also significant. First, the directional changes in cardiac volumes during supine exercise require reevaluation. Recent studies[25,26] using single plane echocardiography to determine ventricular volume found no significant changes in end-diastolic dimensions during mild to moderate supine exercise. Other investigators,[27,35] using radionuclide angiography, reported an increase in end-diastolic volume during erect exercise in normal subjects. However, end-systolic volume generally decreases,[25,27,35] correlating with an augmented ejection fraction. Thus, considerable data suggest that the volume of intracavitary blood does not change in the direction usually considered during the period of cardiac electrical activation.

Second, the orientation of activation waves are probably not purely radial nor purely tangential. Some data[36,37] suggest that wavefront propagation is influenced by cardiac fiber orientation. Because free wall myocytes tend to lie parallel to endocardial and epicardial surfaces, with differing orientations at various intramural planes,[38] even free wall activation would not be purely radial. Similarly, activation of basal segments would certainly be partially radial to result in the recorded epicardial QRS configurations.[33,34] Thus, the two premises underlying simple application of the "Brody effect" to exercise electrocardiography may be questioned.

Augmented atrial repolarization forces during exercise: Another mechanism, related to the data presented here, is based on the augmented atrial repolarization forces generated during exercise. This hypothesis is based on observations that (1) atrial repo-

larization forces (T_a) are of opposite polarity to P wave potentials (that is, negative over much of the anterior thorax[18]) and (2) atrial repolarization proceeds into and possibly throughout the time of ventricular excitation.[39] Thus, the QRS complex would be superimposed on a negative field, causing a reduction in the magnitudes of all wave segments. It is only reasonable to assume that this mechanism is operative during at least the early portion of the QRS complex; P-R segment forces during exercise (Fig. 6) should not be expected to cease abruptly at the onset of ventricular activation.

Aspects of current data also support this proposal. Isopotential difference maps during the P-R segment (Fig. 6) are similar in pattern to those observed during the QRS complex (Fig. 4). This similarity would be expected if the same effect (that is, atrial repolarization) were the cause of both distributions. The predominant negativity of these distributions resulted in a decrease in both peak positive and peak negative QRS potentials (Fig. 5).

A second finding related to this mechanism is the change in overall QRS amplitude during exercise (Fig. 5). At first glance, it would seem that superposition of the QRS complex on a negatively displaced baseline due to atrial repolarization would equally reduce R and S wave magnitudes. Thus, QRS amplitude should remain constant. However, R and S waves recorded at any one site are sensed at different instants and hence will be altered differently, as determined by the time course of the intensity of the causative effect.

However, this time course of intensity of the exercise effect is contrary to that described for atrial T waves. In Figure 8, the exercise-induced negativity followed a roughly symmetric time course, being of relatively low amplitude during the P-R segment, increasing abruptly and peaking during the QRS complex, and then decreasing during the S-T segment. Data from canine[39] and clinical[40,41] studies have suggested a more gradual time course of T_a strength.

Implications: Thus, neither of the two most commonly suggested causes of QRS changes (blood volume or mass and augmented atrial repolarization forces) are solely responsible for the observed effects of exercise on the reported isopotential distributions. Whether combinations of these two mechanisms or others are operative should be further explored.

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Improved Catheter for Regional Coronary Sinus Flow and Metabolic Studies

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An improved coronary sinus catheter has been developed whose enhanced flexibility facilitates catheterization of the great cardiac vein. It allows simultaneous thermodilution measurement of blood flow in the great cardiac vein and proximal coronary sinus, easy withdrawal of blood from both sites and bipolar atrial pacing from the proximal coronary sinus. The accuracy of flow measurement with this catheter has been validated by in vitro testing, and the catheter has been used successfully in eight patients. The advantages of this improved catheter over the existing coronary sinus thermodilution catheter are discussed.

Use of the thermodilution technique to provide safe and easy measurement of human coronary sinus blood flow has been widely applied since its introduction in 1971 by Ganz et al.[1] The Ganz catheter (Wilton Webster Labs, Altadena, California) has undergone only limited modification since that time,[2] despite the several difficulties it presents in the performance of regional studies of coronary sinus blood flow and metabolism. To overcome these difficulties (slow and tedious blood sampling, sampling from only the site of the great cardiac vein, and an overall design that makes catheterization of the more anterior portions of the great cardiac vein difficult) we have developed an improved coronary sinus catheter in conjunction with Electro-catheter Corporation, Rahway, New Jersey.

Methods

Catheter design: The catheter is 60 cm in length and 2.3 mm (7 French) in diameter. At the time of its extrusion from somewhat stiffened polyvinyl chloride, the catheter is partitioned into four discrete lumens. One of the two larger lumens is used for blood sampling and injection of thermal indicator at the catheter tip, through a 0.5 mm diameter end hole (Fig. 1). The other large lumen is used for blood sampling from the more proximal coronary sinus through a side hole located 4 cm from the catheter tip. One of the two smaller lumens contains the leads of the two thermistors used for flow measurement. These are mounted flush with the catheter surface at distances of 0.5 and 3.5 cm, respectively, from the catheter tip. The final lumen contains the leads for the two 2 mm platinum pacing electrodes mounted on the catheter surface adjacent to the proximal sampling port and thermistor. A third thermistor (not shown in the figure) is used to measure the temperature of the injectate just before its entry into the catheter.

Signals from the coronary sinus, great cardiac vein and injectate thermistors are processed with use of a specially built three channel Wheatstone bridge, whose output is amplified and recorded on a multichannel recorder. Just before insertion of the catheter, the catheter tip and injectate thermistors are immersed in sterile saline solution at approximately room and body temperatures. Adjustment of the bridge controls at these temperatures provides identical signal output from each of the three thermistors, linearly related to temperature over the range of 20° to 40° C.

Catheterization technique: The catheter is introduced into the venous circulation by percutaneous insertion of a 7 French sheath and dilator into the

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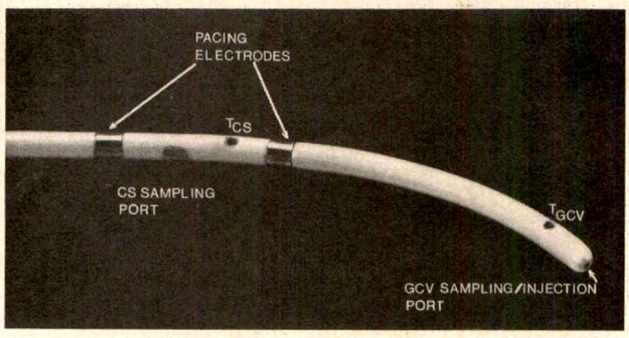


FIGURE 1. Catheter tip design. Pacing electrodes are 1.5 cm apart. The coronary sinus (CS) sampling port is located 4 cm from the great cardiac vein (GCV) sampling port. T_{CS} and T_{GCV} are coronary sinus and great cardiac vein thermistors, respectively.

right internal jugular vein. With use of fluoroscopy and continuous pressure monitoring of the catheter tip lumen, the catheter is usually advanced just across the tricuspid valve into the right ventricle. A combination of slight posterior rotation and gradual withdrawal of the catheter until right atrial pressure is observed leads to engagement of the coronary sinus. This is recognized by continued presence of a right atrial waveform during advancement of the catheter across the cardiac silhouette and the characteristic "double bounce"

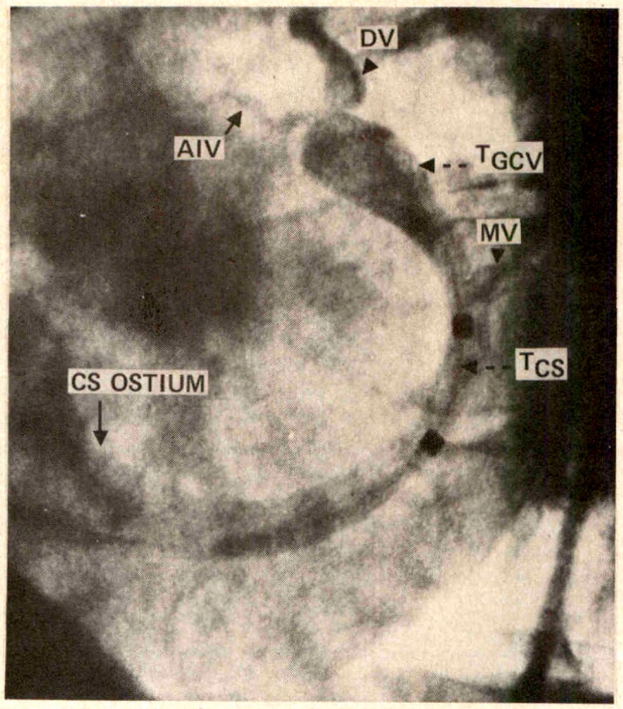


FIGURE 2. Coronary venous anatomy (left anterior oblique projection) visualized during contrast injection through the great cardiac vein port of the catheter. AIV = anterior interventricular vein; CS OSTIUM = coronary sinus ostium; DV = diagonal vein; MV = marginal vein. The position of the thermistors in the great cardiac vein (T_{GCV}) and coronary sinus (T_{CS}) is indicated (see Fig. 1).

motion of a catheter located in the coronary sinus. Although the catheter usually advances directly into the great cardiac vein, it may occasionally enter a venous tributary (posterior interventricular or marginal vein). This error is corrected by partial withdrawal and readvancement of the catheter, or by partial withdrawal of the catheter and cautious advancement of the soft end of a guide wire (0.018 inch [0.046 cm] straight or J guide) into the great cardiac vein.[3] Gentle manual injection of 2 to 5 ml of contrast material (Renografin-76®) through the tip lumen confirms the position of the catheter relative to the coronary sinus ostium and side branches (Fig. 2), and ensures that the tip is not wedged in the anterior interventricular or diagonal veins. Tip wedging should also be suspected when advancement of the catheter in the coronary sinus produces a ventricularized pressure waveform at the tip lumen. Care is taken to avoid movement of the catheter between serial flow measurements, although spontaneous movement is minimized by the position of the catheter well within the cardiac venous system.[2] The proximal thermistor is positioned at least 1 to 2 cm inside the coronary sinus ostium to avoid potential sensing of right atrial blood reflux.[4] When performing measurements over a period of more than 1 hour, we administer heparin to our patients for the period of study.

All patients gave informed consent for use of this catheter under the supervision of the Stanford University Human Subjects Committee.

Flow measurement: For measurement of regional flow, body temperature (T_B) is recorded from the catheter thermistors; then, room temperature injectate (either 5 percent dextrose in water or normal saline solution) is injected through the distal lumen for 20 to 30 seconds at a constant rate of 50 ml/min with use of a Harvard pump. During this injection, the catheter thermistors measure the temperature of the blood-injectate mixture at the sites of the great cardiac vein (T_MGCV) and coronary sinus (T_MCS), and the separate injectate thermistor measures the temperature of the injectate (T_I) (Fig. 3). Flow at the site of the great cardiac vein or coronary sinus is calculated using the specific values of T_MGCV or T_MCS in place of T_M in the formula:

$$\text{Flow} = \frac{T_M - T_I}{T_B - T_M} \times F_I \times C \times 1.05,$$

where F_I is the injectate flow rate, C is a constant based on the thermal properties of blood and injectate (C = 1.08 for 5 percent dextrose; C = 1.19 for normal saline solution injectate),[1] and 1.05 is a factor based on the in vitro calibration data given later. Because the thermistors have identical outputs over the range between room and body temperatures, the relative values of $(T_M - T_I)$ and $(T_B - T_M)$ can be measured in millimeters directly from the paper printout without the need to convert the output signals into actual temperature values.

Catheter calibration: In vitro calibration of the catheter was performed by comparison of thermodilution flow measurements with actual timed volumetric collections of 37° C water flowing through Tygon® tubing (internal diameter 7 mm) in which the thermodilution catheter was inserted.[1] Because water was used as both the injectate and flow fluid, a value of 1.0 was used for C. Data for each thermistor (T_{GCV}, T_{CS}) were separately compared with volumetric flow by linear regression.

Results

At injectate flow rates of 52 to 53 ml/mm, calculated thermodilution flows were linearly related to volumetric

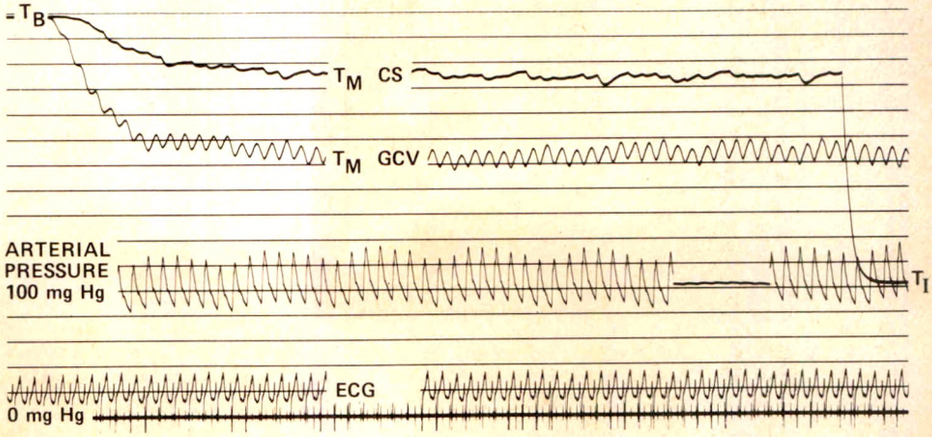


FIGURE 3. Strip chart recording of regional flow measurement during coronary sinus pacing at a rate of 140 beats/min. Body temperature (T_B), injectate temperature (T_I), and the temperatures of the blood-injectate mixture at the great cardiac vein (T_M GCV) and coronary sinus (T_M CS) thermistors are shown. Calculated flows are 55 ml/min in the great cardiac vein and 178 ml/min in the coronary sinus. Arterial pressures (phasic and mean) and surface electrocardiogram (ECG) are recorded simultaneously with flow measurement.

flow over the range of 0 to 250 ml/min for the great cardiac vein (distal) thermistor and 0 to 350 ml/min for the proximal (coronary sinus) thermistor (Fig. 4). Extensive animal and human validation of the thermodilution technique of coronary venous flow measurement has previously been performed by Ganz[1] and Pepine[2] and their co-workers using the functionally similar Ganz catheter.[1,2]

To date, our improved coronary sinus catheter has been inserted in eight patients. Catheterization of the great cardiac vein, often to the takeoff of the anterior interventricular vein, has been possible in all cases (Fig. 2). Easy regional blood sampling and stable regional flow measurements have been performed for periods of up to 15 hours. Great cardiac vein and coronary sinus blood flows at rest were within the range previously reported with use of the Ganz catheter.[1,2] No episodes of perforation, tamponade or serious cardiac arrhythmia resulted from its use in our patients. Tip wedging in the anterior interventricular vein occurred in three cases, was detected by ventricularization of the tip pressure or the initial contrast injection, and was corrected without sequelae by slight withdrawal of the catheter.

Discussion

The combination of thermodilution measurement of human coronary venous outflow with chemical analysis of arterial and coronary venous blood has proved a valuable tool in the investigation of ischemic heart disease. When care is taken to avoid technical pitfalls such as catheter movement and the sampling of right atrial blood reflux, thermodilution measurements of coronary venous flow are widely accepted as accurate relative measurements of global myocardial blood flow.[2,5] The sensitivity of such studies is enhanced by the ability to make regional measurements[3,6,7] in the great cardiac vein (reflecting anterior left ventricular drainage) and the more proximal coronary sinus (reflecting anterior as well as posterolateral left ventricular

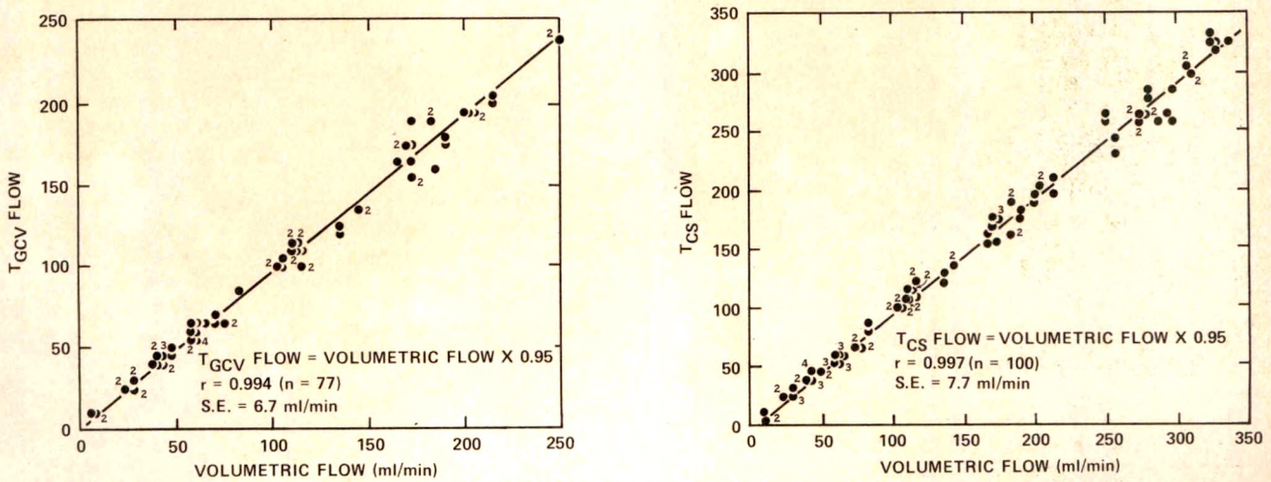


FIGURE 4. Graphs of in vitro calibration data of (**left**) great cardiac vein thermistor (T_{GCV}) flow versus volumetric flow and (**right**) of coronary sinus thermistor (T_{CS}) flow versus volumetric flow. Numbers 2, 3 and 4 = number of values at each datum point.

drainage), particularly when regional variation in myocardial blood supply is present as in coronary artery disease or coronary spasm. Although such regional flow measurements have been reported using the Ganz catheter,[1,2] this catheter can obtain blood samples only from the great cardiac vein site, and then only by slow withdrawal of the sample. To obtain blood samples from the proximal coronary sinus site, the user of this catheter must insert a second catheter into the coronary sinus,[2,3] adding to the difficulty of the study.

In development of our improved catheter, we have sought to facilitate catheterization of the great cardiac vein and to allow regional determinations of both cardiac venous flow and metabolism using a single catheter. These goals have been met by alterations in the internal structure of the catheter, enhanced flexibility and the use of an end hole injection site that allows the passage of a guide wire to aid positioning of the catheter. The end hole design facilitates the detection of tip wedging in the anterior interventricular or diagonal veins, which would have been overlooked in the past because the injection port of the Ganz catheter is located 1 cm proximal to the catheter tip.[2] Further development of the catheter is now in progress to produce a range of interthermistor distances to match variations in coronary venous anatomy, and to incorporate additional measurement capabilities such as fiberoptic oximetry into the current catheter.

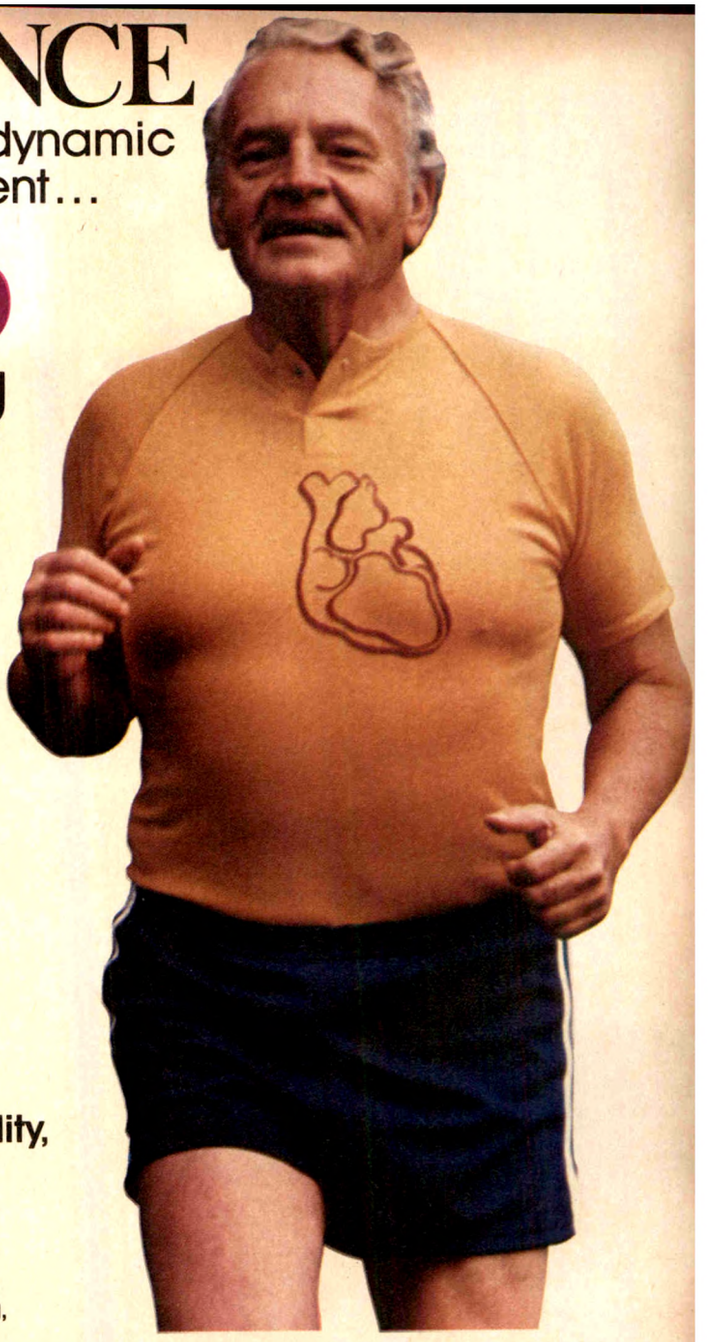
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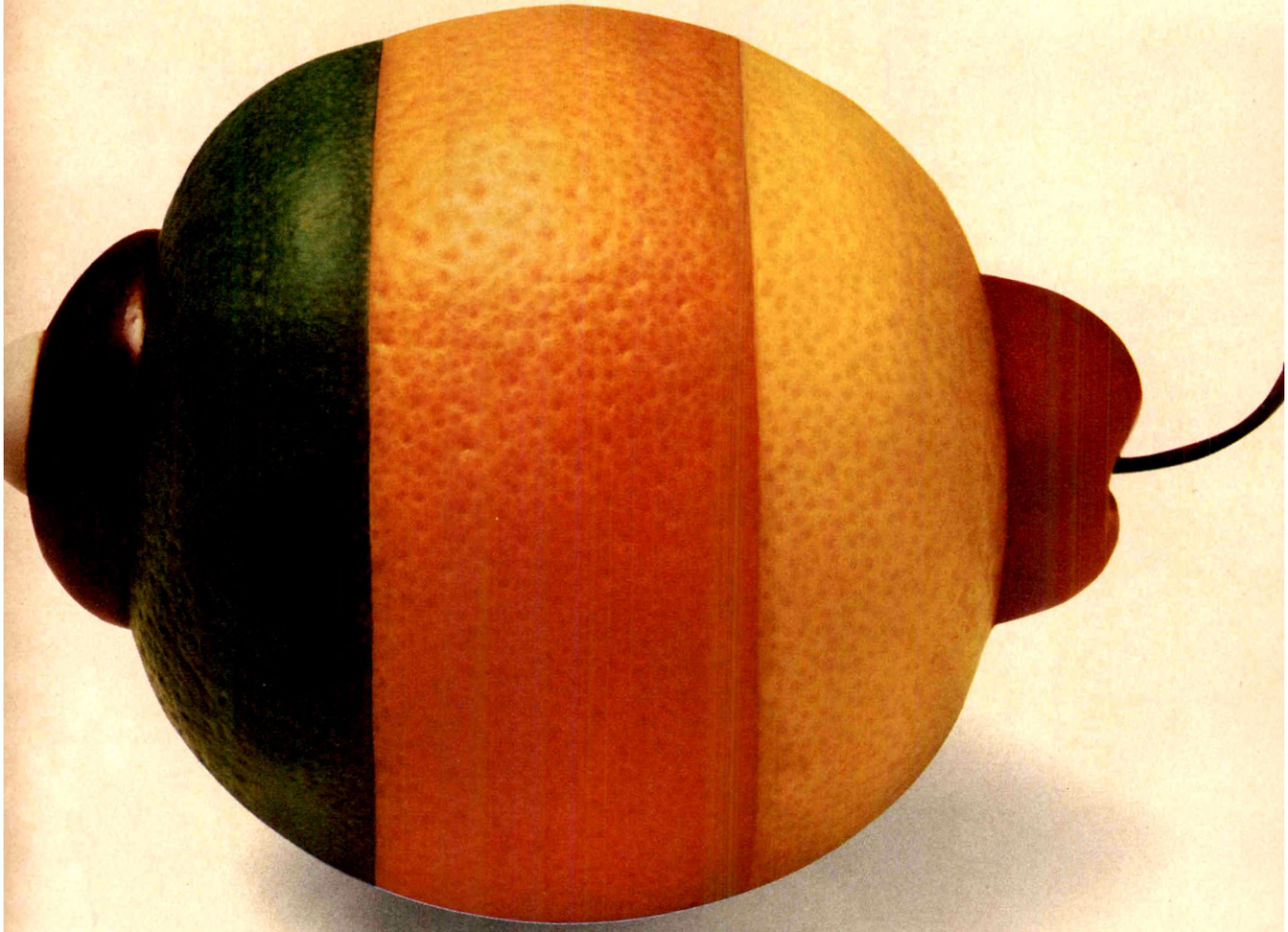
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DESCRIPTION:
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INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

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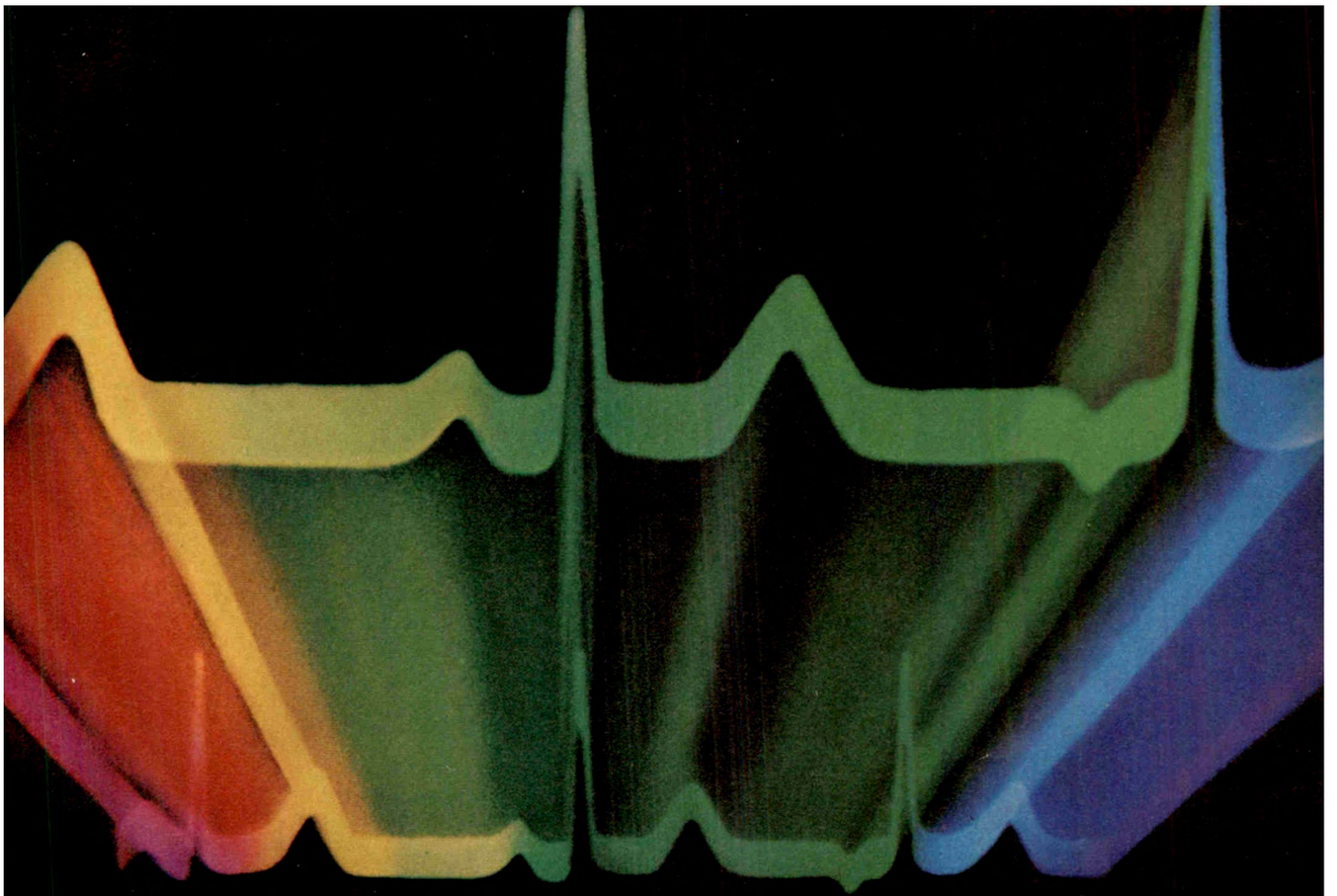
CONTRAINDICATIONS:
Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening.
Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.
Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.
Idiosyncrasy or hypersensitivity to quinidine.

WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

PRECAUTIONS:
The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.
Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.
It should be administered cautiously, if at all, to senile patients.
Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.

ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.
Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.
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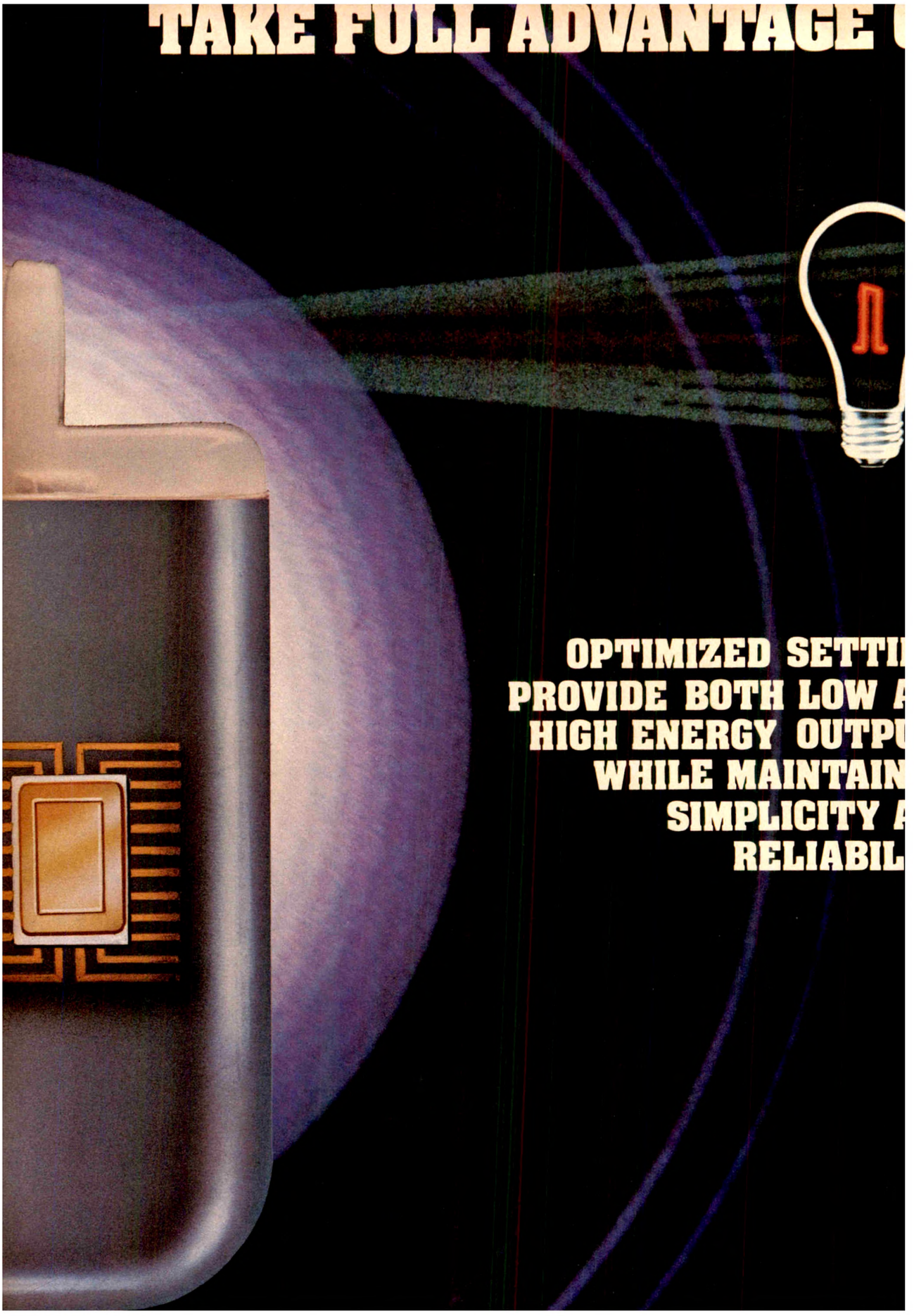
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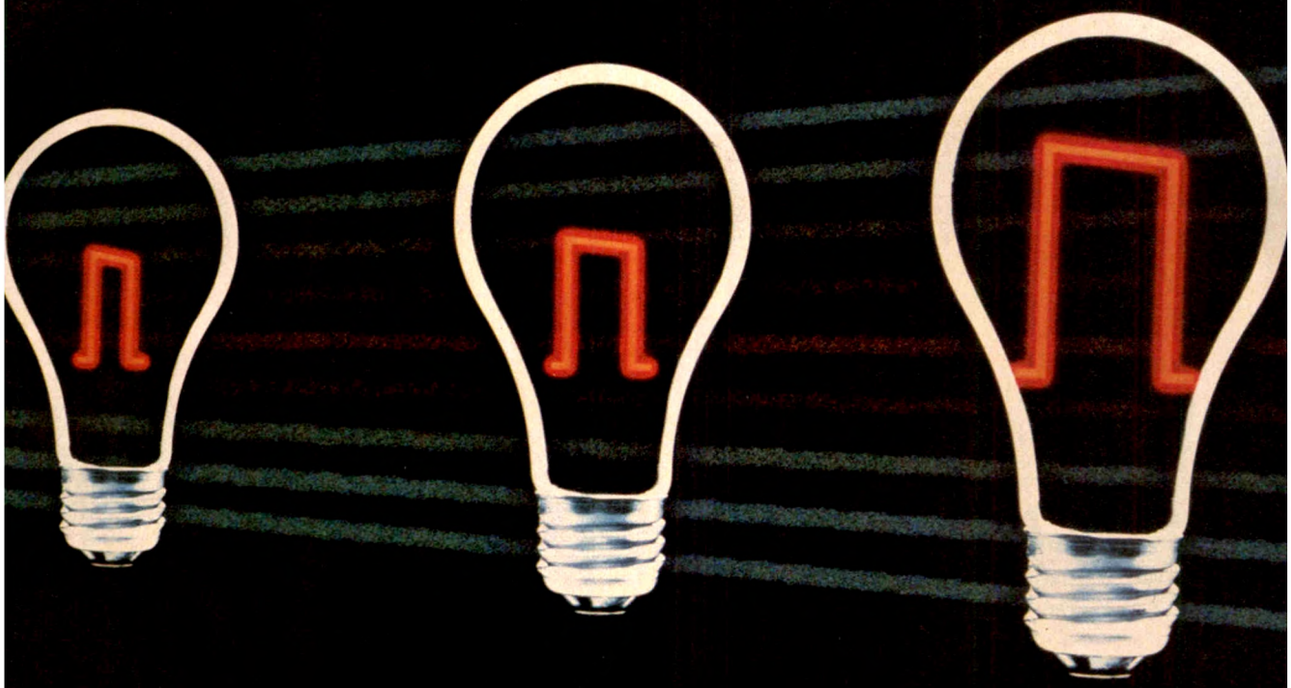
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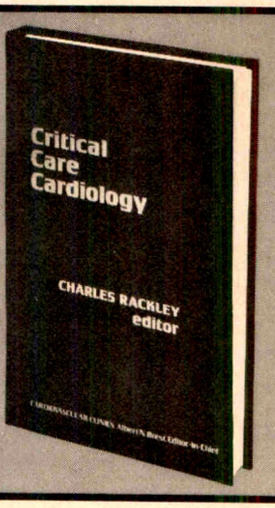
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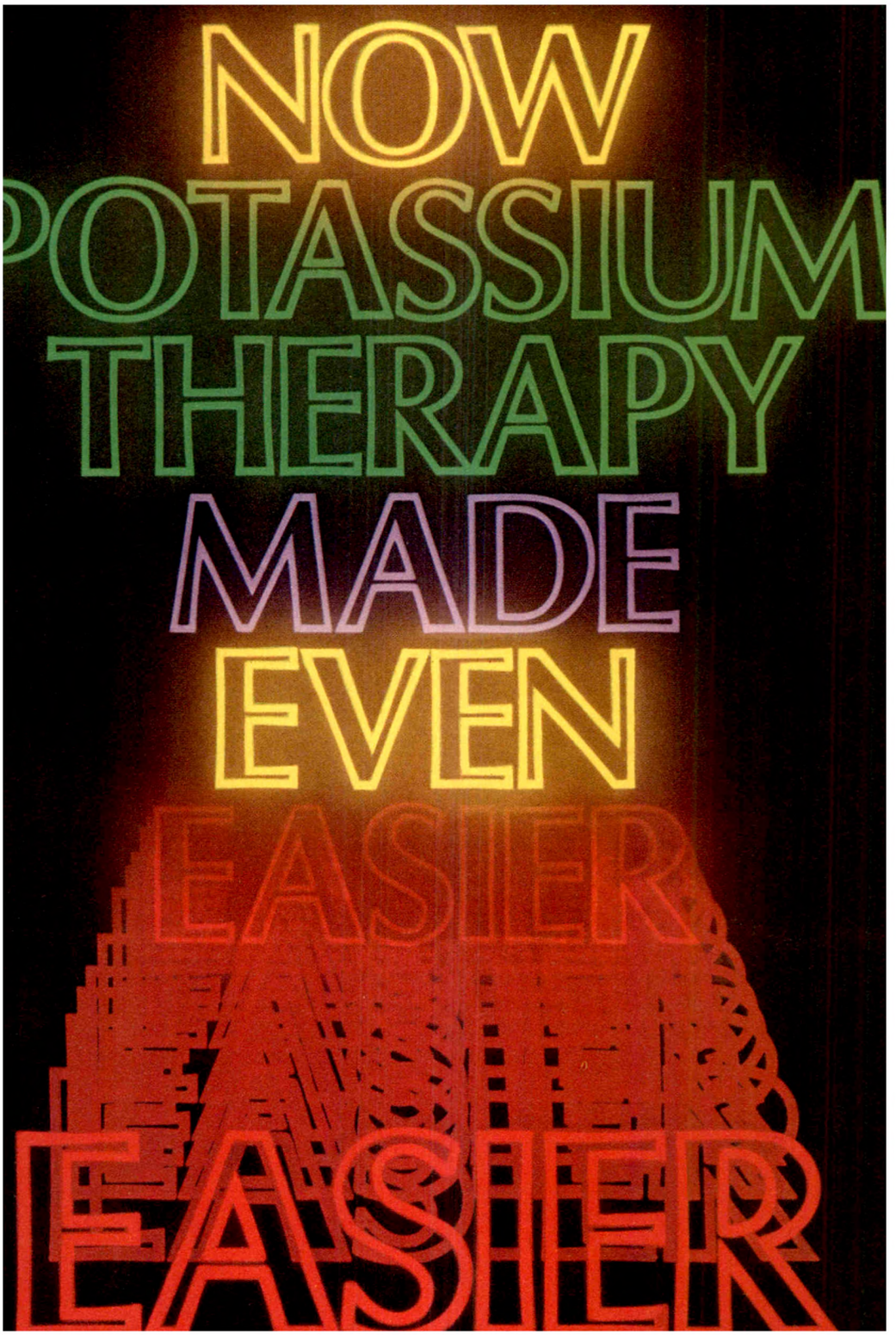
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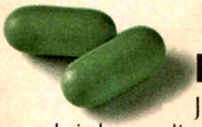
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Description: Kaon Cl™-10 mEq is a sugar coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) th with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cas associated with wax-matrix tablets have been reported both in foreign countries and in t United States. In addition, perhaps because the wax-matrix preparations are not enter coated and release potassium in the stomach, there have been reports of upper gastro testinal bleeding associated with these products. The total number of gastrointesti lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be d continued immediately and the possibility of bowel obstruction or perforation considered severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated w an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassi acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrati hypokalemia in a patient with a clinical history suggesting some cause for potassium dep tion. In interpreting the serum potassium level, the physician should bear in mind that acu alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassiu while acute acidosis per se can increase the serum potassium concentration into the norm range even in the presence of a reduced total body potassium. The treatment of potassiu depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requir careful attention to acid-base balance and appropriate monitoring of serum electrolytes, t electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are na sea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation the gastrointestinal tract and are best managed by diluting the preparation further, taking t dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings a Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretc mechanisms for potassium rarely causes serious hyperkalemia. However, if excretc mechanisms are impaired or if potassium is administered too rapidly intravenously, pote tially fatal hyperkalemia can result (see Contraindications and Warnings). It is important recognize that hyperkalemia is usually asymptomatic and may be manifested only by increased serum potassium concentration and characteristic electrocardiographic chang (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the interval). Late manifestations include muscle-paralysis and cardiovascular collapse fr cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-spari diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10- units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

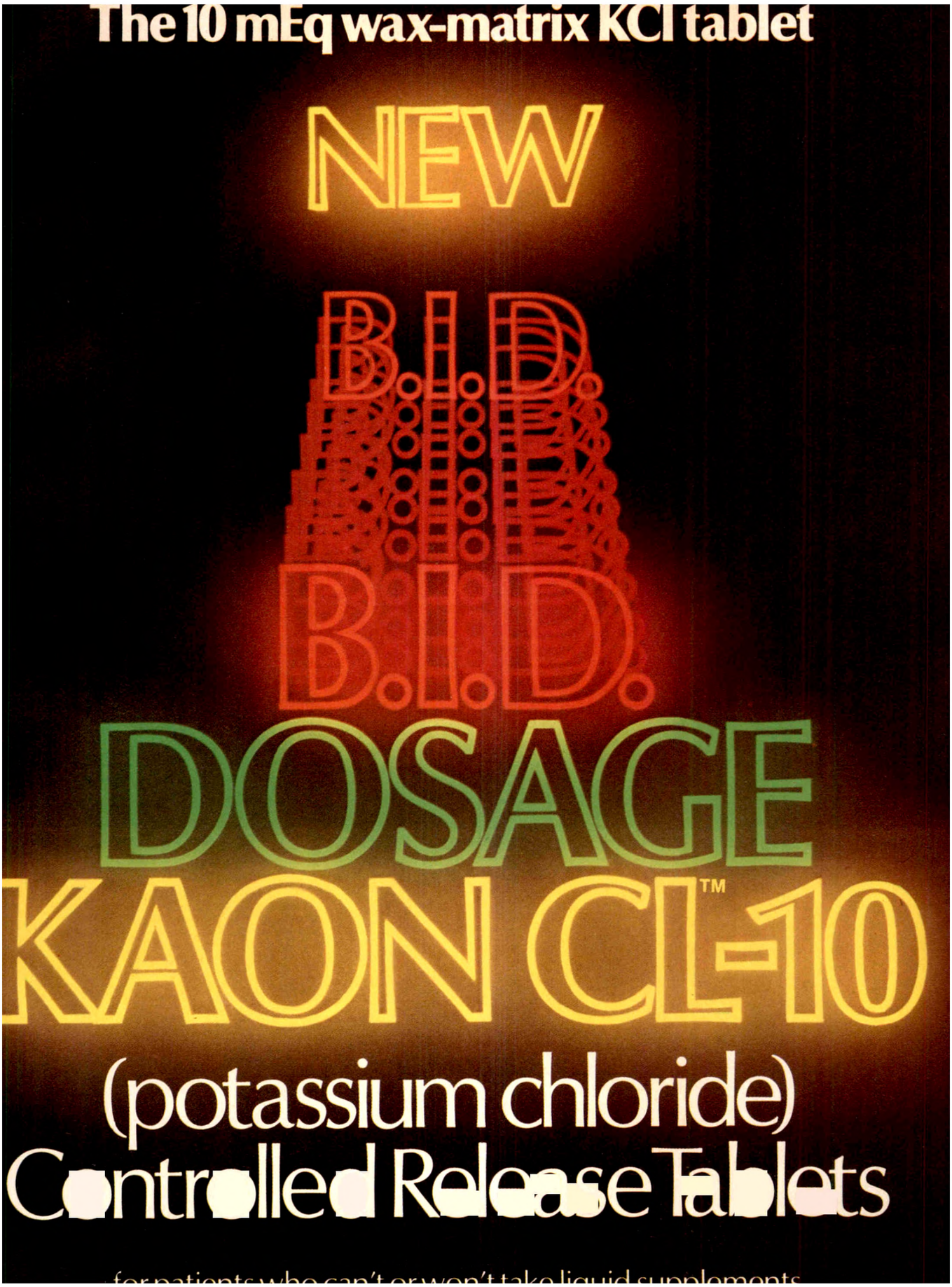
In treating hyperkalemia, it should be recalled that in patients who have been stabilized digitalis, too rapid a lowering of the serum potassium concentration can produce digita toxicity.

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Management of Aortic Arch Interruption With Prostaglandin E_1 Infusion and Microporous Expanded Polytetrafluoroethylene Grafts

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Prostaglandin E_1 infusion and a microporous expanded polytetrafluoroethylene graft were used in the management of eight infants, all less than 4 days old, with interruption of the aortic arch. Five of the six infants receiving prostaglandin E_1 responded dramatically to this therapy, with return of lower limb pulses and lessening of metabolic acidosis. There were no adverse effects attributable to the prostaglandin E_1 infusion. Seven infants subsequently underwent aortic reconstruction with a polytetrafluoroethylene graft. There were no operative deaths, and in up to 3 years of follow-up of these patients, graft obstruction occurred in only one patient and this graft was successfully revised. The long-term mortality rate was high (62 percent); all deaths but one were attributable either to the palliation or to the total correction of the associated cardiac malformations.

Interruption of the aortic arch is a rare vascular malformation that typically results in severe congestive heart failure and acidosis during the 1st week of life. Three locations of the arch interruption have been described: distal to the left subclavian artery (type A); distal to the left common carotid artery (type B); and between the innominate and left common carotid arteries (type C)[1]. Type B is slightly more common than type A and together these two types constitute approximately 95 percent of the reported cases.[2] In almost all cases of arch interruption, there are associated malformations, most commonly ventricular septal defect, aortopulmonary window or truncus arteriosus. A patent ductus arteriosus initially supplies blood to the distal aorta from the main pulmonary artery, and clinical deterioration invariably occurs as the ductus closes. Despite recent case reports of successful surgical palliation[2–7] and even total correction[8–12] of these infants' malformations, the mortality rate remains about 70 percent in the 1st week of life.[13]

In an effort to reduce this neonatal mortality, we recently utilized prostaglandin E_1 for initial management and a polytetrafluoroethylene graft for anatomic correction in infants with interruption of the aortic arch. Prostaglandin E_1 has recently been shown to maintain ductus patency,[14] and in infants with an interrupted aortic arch infusion of this agent allows for continued blood flow from the pulmonary artery to the thoracic aorta, thereby maintaining distal aortic perfusion. The recently developed polytetrafluoroethylene graft has allowed for successful shunting of small caliber blood vessels and these grafts have been associated with much improved patency rates when compared with previously available prosthetic grafts.

Methods

Patients: Eight infants with interruption of the aortic arch were admitted and underwent diagnostic cardiac catheterization at The Johns Hopkins Hospital between December 1976 and September 1979. The clinical data on these infants are shown in Table I. All infants presented in the first 3 days of life. Two had

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TABLE I

Clinical Information in Eight Infants With Interrupted Aortic Arch

Case	Cardiac Diagnosis	Sex	Age at Diagnosis (days)	Weight (kg)	Arterial pH Before PGE_1	Arterial pH After PGE_1	Duration of PGE_1 Infusion (h)	Operation
1	Type B interruption, VSD, PDA	M	1	3.5	6.85	. . .	. . .	5 mm graft, PDA ligation, PA band (two stage)
2	Type B interruption, hypoplastic aorta and aortic valve, VSD, PDA	F	1	2.5	7.18	7.40	12	None
3	Type B interruption, type A4 truncus arteriosus, PDA	M	3	2.7	7.30	7.45	7	5 mm graft, PA band, PDA ligation
4	Type A interruption, VSD, PDA	M	3	3.5	7.35	. . .	. . .	5 mm graft, PA band, PDA ligation
5	Type B interruption, AP window, PDA	M	2	2.6	7.30	7.45	36	5 mm graft
6	Type B interruption, VSD, PDA	F	2	3.1	7.05	7.34	11	5 mm graft, PA band, PDA ligation
7	Type A interruption, VSD, PDA	M	2	3.6	7.21	7.31	10	5 mm graft, PA band, PDA ligation
8	Type A interruption, VSD, PDA	F	2	3.6	6.83	7.12	3	5 mm graft, PA band, PDA ligation

AP = aortopulmonary; PA = pulmonary artery; PDA = patent ductus arteriosus; PGE_1 = prostaglandin E_1; VSD = ventricular septal defect.

type A interruption; the remaining six had a type B defect (Fig. 1). All but two infants had an associated ventricular septal defect. One of the latter (Patient 3) had an associated type A4 truncus arteriosus[15] and the other (Patient 5) had an aortopulmonary window as well as a patent ductus arteriosus. A markedly hypoplastic aortic anulus and ascending aorta further complicated Case 2. All infants had congestive heart failure and were initially treated with digitalis and diuretic drugs.

Prostaglandin E_1 therapy: Prostaglandin E_1 was not available for infusion in Patient 1 at the time of diagnosis. Of the remaining seven patients, six had significant metabolic acidosis (pH <7.30) as well as congestive heart failure, and were treated with continuous infusion of prostaglandin E_1, 0.1 μg/kg per min intravenously, into either a peripheral or central venous catheter.

Surgical therapy: Surgery was performed in all patients within 36 hours of diagnosis with the exception of the infant (Patient 2) with hypoplasia of the ascending aorta, whose lesion was judged uncorrectable. At operation, a 5 mm tubular polytetrafluoroethylene graft was interposed between either the left common carotid or the left subclavian artery and the descending aorta, depending on the site of the origin of interruption. The patent ductus arteriosus was ligated and the pulmonary artery banded in all patients except the infant with the associated aortopulmonary window.

Results

Response to prostaglandin E_1 therapy: In the six acidotic infants, infusion of prostaglandin E_1 was maintained for an average of 13 hours (range 3 to 36) and was terminated after the completion of graft placement. Hypotension, bradycardia, fever and muscle twitching, previously reported[16] adverse effects of prostaglandin E_1, were not noted in any patient. Five of the six infants had a satisfactory response to the infusion within 30 minutes of its onset, as demonstrated by return of palpable femoral pulses and with blood pressure in the lower limbs becoming equal to that in the right arm. In addition, there was definite amelioration of the metabolic acidosis. The mean arterial pH before infusion of prostaglandin E_1 was 7.14 (range 6.83 to 7.30); after infusion it was 7.34 (range 7.12 to 7.45) (Fig. 2). The condition of one infant (Patient 8), whose initial pH was 6.83, failed to improve even after the infusion was increased to 0.15 μg/kg per min; there was

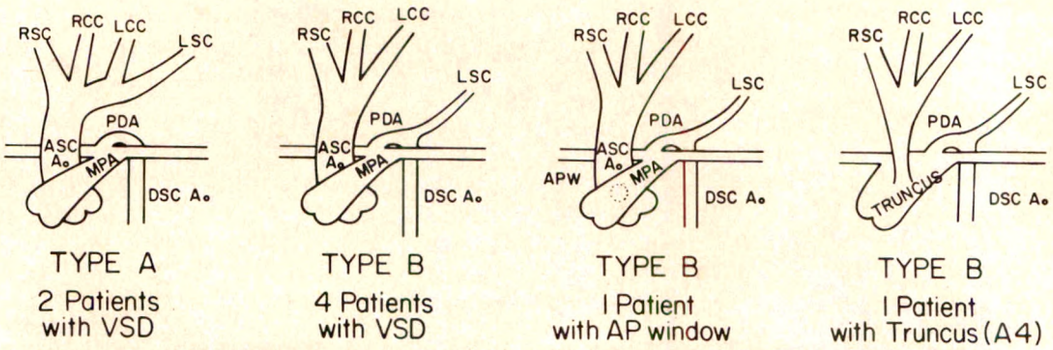


FIGURE 1. Diagrammatic illustrations of the preoperative anatomy of the arch and associated malformations in eight patients. AP = aortopulmonary; APW = aortopulmonary window; ASC Ao = ascending aorta; DSC Ao = descending aorta; LCC = left common carotid artery; LSC = left subclavian artery; MPA = main pulmonary artery; PDA = patent ductus arteriosus; RCC = right common carotid artery; RSC = right subclavian artery; Truncus = truncus arteriosus; VSD = ventricular septal defect.

some increase in the arterial pH, but the infant remained markedly acidotic and femoral pulses were never palpable even after 2 hours of the larger dose of prostaglandin E_1.

Cardiac catheterization findings: At the time of cardiac catheterization, the typical arch appearance as well as a large patent ductus arteriosus with right to left shunting was demonstrated in all but one patient. The exception was the infant (Case 8) who failed to respond to prostaglandin E_1; although the ductus was seen in the angiogram, it was markedly narrowed over its entire length. In all other infants, there was no pressure gradient demonstrated on catheter pullback across the ductus arteriosus from the descending thoracic aorta to the main pulmonary artery. Significant left to right shunting at the ventricular or great vessel level (aortopulmonary window) was also demonstrated in all patients.

Operative results: Seven of the eight infants underwent operation; the condition of one infant with a hypoplastic ascending aorta (Case 2) was considered inoperable and she died at age 3 days, secondary to coagulation abnormalities that had developed before the start of the prostaglandin E_1 infusion. The initial operation for repair of the arch interruption was successful in all patients and, in all but one patient, the pressure gradient between the upper and lower limbs did not exceed 15 mm Hg in the postoperative period.

Complications after operation included transient oliguria (less than 0.5 cc/kg per hour of urinary flow) in five patients, respiratory insufficiency requiring prolonged (more than 5 days) ventilatory support in three patients and persistent severe congestive heart failure in three patients. The infant with the associated aortopulmonary window (Case 5) continued to have severe congestive heart failure and at age 8 days underwent total correction, but died 4 hours after this operation with evidence of severe biventricular failure. The other two children with heart failure underwent cardiac recatheterization 1 month postoperatively; one (Case 1) had an inadequate pulmonary arterial band that was then successfully tightened, and the other infant (Case 3) with the associated type A4 truncus arteriosus had a residual significant obstruction at the left carotid-graft anastomosis, but continued to be managed medically.

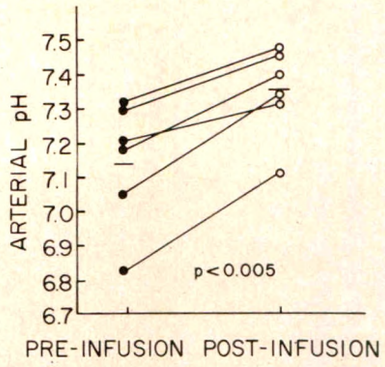


FIGURE 2. Increase in arterial pH after prostaglandin E_1 infusion in six patients. The difference between preinfusion pH (**closed circles**) and postinfusion pH (**open circles**) is significant at a probability (p) level of <0.005 (paired *t* test).

Follow-up: The long-term follow-up period in the six patients who left the hospital ranged from 2 to 34 months (mean 12) (Table II). Figure 3 shows the appearance of the graft in Patient 4 one year postoperatively. Two children died 6 months postoperatively, one (Case 6) with overwhelming bacterial sepsis unrelated to her heart disease. At autopsy, no evidence for an immune deficiency could be established. The other patient (Case 7) died suddenly and at autopsy had a markedly stenotic pulmonary artery at the site of the band with evidence of severe right ventricular hypertrophy. Successful closure of a ventricular septal defect and band takedown was performed in one child (Case 1) at age 1 year. A second child (Case 4) died after intracardiac surgery at age 1 year; death was believed to be caused by right ventricular dysfunction.

Patient 3, the child with the associated truncus arteriosus who had residual obstruction at the carotid artery-graft anastomosis, underwent graft replacement at age 2 years without difficulty. After insertion of a 6 mm polytetrafluoroethylene graft, there was no residual pressure gradient from the ascending to the descending

TABLE II

Follow-Up Data in Eight Patients

Case	Duration of Follow-Up Study (mo)	Gradient Across Graft* (mm Hg)	Subsequent Operation	Status
1	35	10	14 mo: VSD closure, band takedown	Alive
2	3 days	. . .	None	Died
3	26	70	25 mo: Graft replacement (6 mm)	Alive, no residual gradient
4	12	10	12 mo: VSD closure, band takedown	Died 3 days postop
5	8 days	0	8 days: Aorto-pulmonary window repair	Died 4 h postop
6	6	0	1 mo: Band revision	Died 6 mo postop, sepsis
7	6	10	None	Died 6 mo postop, ?RV failure
8	4	10	None	Alive

* Difference between upper and lower limb systolic blood pressures as measured with the Doppler technique at the time of the last follow-up study or at postoperative cardiac catheterization.

Postop = postoperative; RV = right ventricular; VSD = ventricular septal defect.

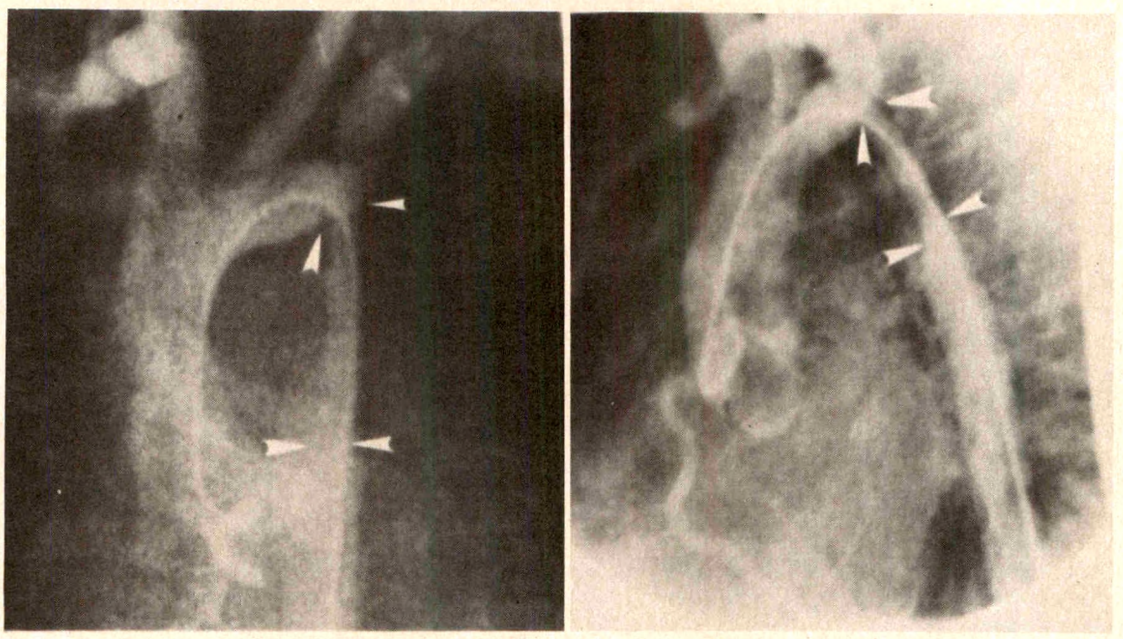


FIGURE 3. Case 4. Aortogram in the anteroposterior (**left**) and lateral (**right**) projections performed 1 year postoperatively. The graft anastomoses to the left subclavian artery (**above**) and the descending aorta (**below**) (**arrows**) are slightly narrowed, and the pressure gradient at cardiac catheterization measured 10 mm Hg.

aorta. In no other child, including those who died, was there evidence of progressive anastomotic or graft obstruction during the follow-up period.

Discussion

The high mortality rate associated with interruption of the aortic arch is due in part to (1) the profound metabolic acidosis that occurs at the time of spontaneous closure of the ductus arteriosus, (2) the difficulty in obtaining a satisfactory anatomic repair, and (3) the severity of the associated cardiac malformations. Recent medical and surgical advances have facilitated the management of these critically ill infants.

Role of prostaglandin E_1 therapy: Prostaglandin E_1 dilates the ductus arteriosus in newborn animals and human beings[13,14,16,17] and has been used extensively in the past 5 years in the management of infants with ductus-dependent cyanotic congenital heart diseases.[18–20] Because, in interruption of the aortic arch, circulation to the distal aorta is dependent on blood flow through the ductus arteriosus from the main pulmonary artery, prostaglandin E_1 can provide critical support in this condition as well. Reopening or dilatation of the ductus restores pulsatile flow to the descending aorta, usually with well saturated blood because of the associated large left to right shunts. This has been demonstrated clinically by several investigators.[21–23] Heyman et al.[23] found an increase in pulsatile thoracic aortic pressure in six of seven infants treated with prostaglandin E_1. The arterial pH was at least 7.30 in all infants and no change was noted after infusion of prostaglandin E_1.

In five of the six infants in our series with poor cardiac output and metabolic acidosis, the response to prostaglandin E_1 was dramatic. Femoral pulses returned, peripheral vasoconstriction abated, and metabolic acidosis lessened as a result of increased perfusion of the viscera and skeletal muscle. The major difference among the five infants who responded to prostaglandin E_1 infusion and the one infant whose ductus was not apparently relaxed by the infusion was the lower initial arterial pH in the nonresponding infant. Age at the time of diagnosis, duration of symptoms and anatomic findings were otherwise similar. Previous reports[18–20] of ductal response to prostaglandin E_1 infusion have not noted a poorer response to the drug in infants with profound acidosis.

Although ductal dilatation improved the condition of the majority of infants in this series, complications with its use have been reported and its long-term effects are unknown. In some infants with interruption of the aortic arch, like our Patient 4, the earlier recognition and transport of neonates with congenital heart disease may result in diagnosis of their condition before ductal closure is signaled by the onset of acidosis. In these infants, ductal manipulation by prostaglandin E_1 infusion would not be necessary before operation.

Role of early aortic arch grafting and other surgical procedures: A variety of surgical approaches to arch interruption have been suggested in recent reports. Palliative procedures have included pulmonary arterial banding either with direct anastomosis of the proximal and distal aorta,[13] or with mobilization of the left common carotid artery or subclavian artery for anastomosis to the descending aorta.[4,7,12] This direct approach to repair is limited by the proximity of the proximal and distal aortic segments as well as by the size of the peripheral vessels involved in the anastomosis. Several groups[2,3] have placed synthetic grafts, usually of Dacron®, between the main pulmonary artery and the

descending aorta, in this way creating an artificial ductus arteriosus. Grafts have also been interposed between the proximal and distal aorta.[13,24] Total correction of this complex anomaly, including closure of associated ventricular septal defect, has been accomplished in four infants using profound hypothermia with total circulatory arrest.[8–11]

The placement of a polytetrafluoroethylene graft between a branch of the proximal aortic segment and the distal aorta as described in this report allows for a more physiologically sound redirection of distal systemic blood flow than does shunt placement from the pulmonary artery to the aorta. Furthermore, there has been a small incidence of anastomotic obstruction at the time of graft placement and excellent long-term graft patency using this graft. This experience contrasts with that reported by Allard et al.[24] who described poor long-term graft patency when small caliber Dacron grafts were used. It is not known if the use of a 4 mm polytetrafluoroethylene graft would impair long-term graft patency in infants in whom a larger graft was not feasible.

The successful restoration of aortic continuity in all seven of the neonates operated on in this series has been gratifying. One factor in this improved operative mortality was the improved medical status of the infants at cardiac catheterization and at operation. Prostaglandin E_1 therapy resulted in ductal dilatation with enhancement of cardiac output and amelioration of the acidosis in all but one of those surgically treated infants. However, overall mortality (five of eight) in this group of infants remains quite high, and is related to the complexity of the associated lesions, their initial palliation and the operative difficulties encountered during definitive surgical repair. The long-term difficulties with pulmonary arterial banding, including pulmonary arterial distortion and the development of severe right ventricular hypertrophy with right ventricular dysfunction, directly contributed to two of the three late deaths. The marked increase in right ventricular wall thickness found in these infants could be a response peculiar to pulmonary arterial banding when performed in the 1st week of life. At this age, myocardial muscle cells may still be capable of undergoing hyperplasia as well as hypertrophy,[25,26] which may result in greater wall thickness and muscle mass.

In summary prostaglandin E_1 and polytetrafluoroethylene grafts have improved the immediate prognosis for neonates with interruption of the aortic arch. As further long-term follow-up data become available, the age at which graft replacement is necessary and the role of surgical palliation and total correction of the associated lesions will become more clearly defined.

Acknowledgment

We thank the Upjohn Company for providing the prostaglandin E_1.

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Stress-Induced Ventricular Arrhythmia After Repair of Tetralogy of Fallot

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The combination of ventricular arrhythmias found on routine electrocardiography at rest and elevated right ventricular pressures may be associated with sudden death in patients after repair of tetralogy of Fallot. In this study data were reviewed from 104 patients who underwent treadmill exercise testing with a modified Bruce protocol at a mean age of 13.8 years, an average of 7 years after repair of tetralogy of Fallot. The frequency and form of ventricular arrhythmias as manifested in an electrocardiogram at rest as well as before, during and after treadmill exercise tests were tabulated for each patient. Cardiac catheterization was performed within 1 week of the treadmill test in 82 of the 104 patients and the right ventricular systolic pressure, right ventricular end-diastolic pressure, pulmonary arterial systolic pressure and pulmonary to systemic flow (Qp/Qs) ratio were compared in patients with and without ventricular arrhythmias. In 15 (14 percent) of the 104 patients, ventricular arrhythmia was evident in the electrocardiogram at rest and in 31 (30 percent) it was induced by treadmill exercise; 5 of the 15 with arrhythmia at rest had no arrhythmia during exercise. Compared with the remaining 73 patients, the 31 patients who had ventricular arrhythmias during treadmill testing (1) were older (16.2 versus 12.8 years, $p < 0.01$, *t* test) and were tested at a longer interval after repair of tetralogy of Fallot, (2) had greater right ventricular systolic pressure (52.7 versus 41.3 mm Hg, $p < 0.005$), (3) had greater right ventricular end-diastolic pressure (8.0 versus 6.1 mm Hg, $p < 0.001$), and (4) had no difference in pulmonary arterial systolic pressure or Qp/Qs ratio. Uniform premature ventricular complexes were found in 28 patients, multiform premature ventricular complexes in two and ventricular tachycardia in one. Patients whose ventricular arrhythmia appeared with exercise had similar hemodynamic findings to those whose arrhythmia disappeared with exercise. Two patients, each with elevated right ventricular systolic pressure and multiform premature ventricular complexes, had cardiac arrest at home.

It is concluded that (1) treadmill exercise testing is a sensitive method for detecting ventricular arrhythmia in patients after repair of tetralogy of Fallot; (2) ventricular arrhythmia during treadmill exercise is related to abnormal hemodynamic status; (3) multiform premature ventricular complexes, couplets or ventricular tachycardia with exercise testing are highly associated with abnormal hemodynamic status and sudden death; (4) suppression of ventricular arrhythmia with exercise is neither the characteristic nor necessarily the benign response in these patients; and (5) ventricular arrhythmia may be a late developing phenomenon and may increase with longer postoperative intervals. Patients after repair of tetralogy of Fallot should be treated for ventricular arrhythmia detected in the electrocardiogram at rest or during treadmill exercise testing.

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The combination of premature ventricular complexes occurring late postoperatively and persistently abnormal hemodynamic findings may be associated with sudden death in patients after repair of congenital cardiac defects. We recently reported our data on 207 patients who

survived intracardiac repair of tetralogy of Fallot.[1] In the routine electrocardiogram obtained at rest, 21 (10 percent) of these patients had premature ventricular complexes and 8 (38 percent) of the 21 died suddenly. Each of the patients who died had a right ventricular systolic pressure of 70 mm Hg or greater. None had left anterior hemiblock. Because of these findings, as well as those of James et al.,[2] which indicated that exercise-induced ventricular arrhythmia might be predictive of later sudden death, we have routinely been performing exercise tests in patients after intracardiac repair of tetralogy of Fallot.

It was the purpose of this study: (1) to compare the incidence of ventricular arrhythmias found on routine electrocardiography at rest with that found on exercise testing in patients who have had intracardiac repair of tetralogy of Fallot; (2) to determine the relation of ventricular arrhythmia to postoperative hemodynamic status; and (3) to assess the prognosis for patients who have ventricular arrhythmia either on routine electrocardiography or during exercise testing.

Methods

Study patients: We reviewed the records of all patients who had had intracardiac repair of tetralogy of Fallot and found 104 who had a postoperative treadmill test performed between 1974 and 1979. These patients were unselected. Treadmill testing is part of our routine postoperative evaluation of tetralogy of Fallot. In patients who had more than one treadmill test, the test given closest to postoperative cardiac catheterization was examined. All patients had repair of tetralogy of Fallot with ventriculotomy, infundibulectomy and closure of the ventricular septal defect with a patch. Approximately 75 percent of our patients had a transanular outflow patch placed. We did not examine the effect of outflow tract patching on the later development of arrhythmia.

The mean age of the 104 patients at the time of the treadmill test was 13.8 years (range of 5 to 32); this was a mean of 7.0 years after surgery (range 1 month to 18 years). The mean age of the patients at repair of tetralogy of Fallot was 6.8 years (range 2.2 to 14.3). This is a different patient group from the 207 patients recently reported on in a long-term follow-up study of patients after repair of tetralogy of Fallot,[1] with the exception that 17 patients were included in both studies.

Treadmill exercise protocol: A modified Bruce protocol[3] was used in all patients. Before the test, 10 electrodes were placed on the patient to allow recording of three simultaneous electrocardiographic leads. Before exercise, standard 12 lead electrocardiograms were recorded with the patient standing and sitting. These recordings were included as part of the test because they could have disclosed a mild anxiety state as the patient anticipated the impending exercise. During the test, leads II, aVF and V_5 were monitored continually on an oscilloscope. In addition, any arrhythmia noted was stored on the oscilloscopic screen and transcribed immediately onto paper. The postexercise electrocardiogram was monitored and recorded every minute for at least 5 minutes. Data on arrhythmias were tabulated according to when they occurred: before, during or after exercise.

Because so many patients had complete right bundle branch block, which can cause secondary S-T segment and T wave changes, we did not analyze the records for S-T segment shift. The end point of the test occurred when, despite considerable verbal encouragement, a patient refused to exercise further. We did not find it necessary to stop the exercise test in any patient. As an estimate of exercise tolerance, the mean work to exhaustion was calculated for each patient. In addition to the exercise data, the routine electrocardiogram taken with the patient at rest at a time other than the treadmill test (within 1 week) was also examined for ventricular arrhythmias.

Cardiac catheterization: This procedure was performed in 82 of 104 patients within 1 year of the treadmill test.[1] For each patient, the right ventricular systolic pressure, right ventricular end-diastolic pressure, pulmonary arterial systolic pressure and pulmonary to systemic flow ratio were tabulated and related to the exercise and electrocardiographic data.

Statistical analysis: For the patients who died, the interval from the treadmill test to death was recorded; for the other patients, the interval from the treadmill test to the most recent clinic visit was recorded as the follow-up interval. Statistical analysis comparing continuous data for patients was performed using Student's t test. Comparison for categorical data was performed using chi-square analysis. Statistical significance was inferred if the probability of the difference occurring by chance was 0.05 or less.

Results

Arrhythmias

Routine electrocardiogram at rest: Among the 104 patients, 15 had at least one single premature ventricular complex detected on routine electrocardiography (Fig. 1); in 13, the premature complexes were uniform and in two, multiform. One additional patient without premature ventricular complexes had sinus rhythm with type II second degree atrioventricular (A-V) block. Complete right bundle branch block was found in 96 patients (92 percent); 10 (10 percent) of the 104 patients had the combination of complete right bundle branch block and left anterior hemiblock. No patient had left anterior hemiblock without complete right bundle branch block. There was no significant association of premature ventricular complexes with left anterior hemiblock.

Treadmill exercise test: Thirty-one (30 percent) of the 104 patients had ventricular arrhythmia during treadmill testing; 21 patients had at least one single

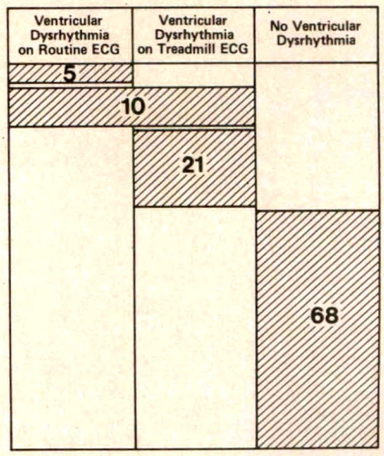


FIGURE 1. Prevalence of ventricular arrhythmia in 104 patients who underwent a treadmill exercise test after intracardiac repair of tetralogy of Fallot. ECG = electrocardiogram.

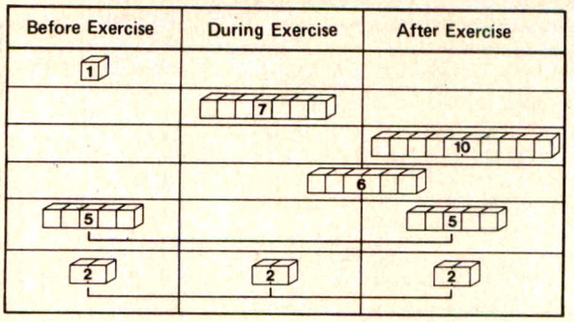
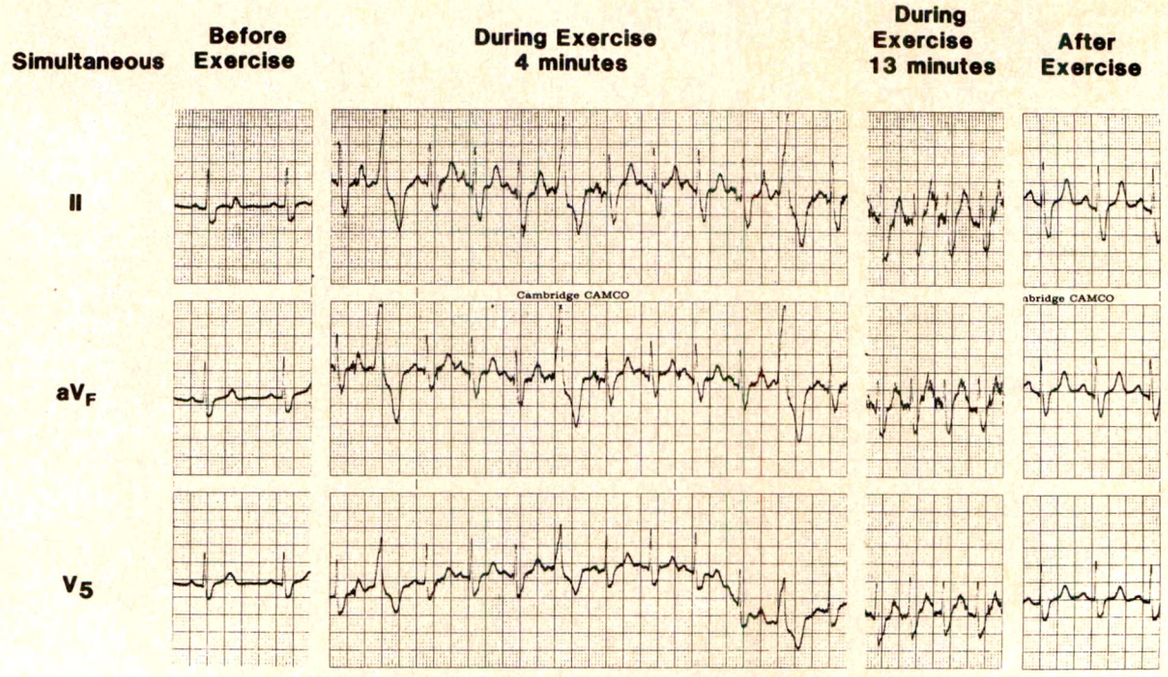


FIGURE 2. Timing of ventricular arrhythmia during treadmill testing. The largest group (10 patients) had no arrhythmia until the postexercise recovery period. In five patients, the arrhythmia occurred before and after exercise but was suppressed during actual exercise.

uniform premature ventricular complex, four had single multiform premature ventricular complexes, four had at least one couplet and two had ventricular tachycardia. In five patients, the premature ventricular complexes found on routine electrocardiography at rest were not reproduced on exercise testing; 10 had ventricular arrhythmia both during routine electrocardiography and during exercise testing; 21 had ventricular arrhythmia only during the test and 68 had no ventricular arrhythmia (Fig. 1). There was no significant association between ventricular arrhythmia found during the exercise test and left anterior hemiblock.

Ventricular arrhythmia occurred during all periods of the exercise test (Fig. 2). It was detected only immediately before exercise in 1 patient, only during the test in 7 patients and only after exercise in 10 patients; 6



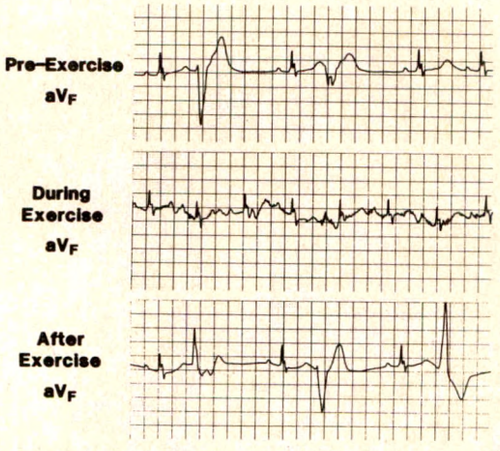


FIGURE 3. Ventricular arrhythmia during treadmill testing. **Top,** the electrocardiogram of this asymptomatic 23 year old woman shows no arrhythmia before exercise but single uniform premature ventricular complexes 4 minutes into the exercise protocol with a heart rate of 116 beats/min. After 13 minutes of exercise, the premature complexes are suppressed with a heart rate of 154 beats/min. No arrhythmia is noted in the postexercise recovery period. **Left,** exercise electrocardiogram of a 32 year old woman who later died suddenly. Before exercise, multiform premature ventricular complexes are found. The sinus rate is 67/min. After 8 minutes of exercise, the sinus rate is 88/min and the premature complexes are suppressed. In the postexercise recovery period, multiform ventricular bigeminy occurs.

patients had ventricular arrhythmia both during and after the test, 5 both before and after but not during exercise and 2 had ventricular arrhythmia before, during and after exercise (Fig. 3).

Two other patients without arrhythmia at rest had premature atrial complexes during the treadmill testing. The one patient with advanced A-V block had an improved A-V conduction ratio (that is from 3:1 to 2:1) with exercise testing but had no ventricular arrhythmia. One of the eight patients without right bundle branch block at rest had functional right bundle branch block with an increase in heart rate during exercise (Fig. 4).

Exercise Tolerance

The exercise tolerance, as measured by the mean work to exhaustion, was within the normal range for our laboratory in all but five patients. Ventricular arrhythmia was found in four of these five patients either on routine electrocardiography or with exercise testing. This finding was compared with the occurrence of ventricular arrhythmia in 27 of the 99 patients with a normal exercise tolerance. Although the numbers are small, there is a statistical relation ($p < 0.05$) between decreased exercise tolerance and ventricular arrhythmia.

Hemodynamics

The hemodynamic data for the 82 patients who underwent cardiac catheterization are summarized in Figure 5. The hemodynamic results are similar to those of our other published series of routine postoperative catheterization in patients after intracardiac repair of tetralogy of Fallot,[1] with approximately 50 percent having an excellent and 30 percent having a poor hemodynamic result. These data indicate that the patients in this study were not selected for treadmill testing on the basis of their hemodynamic status. Systematic evaluation of the degree of pulmonary regurgitation (that is, by velocity catheter) was not carried out at cardiac catheterization; 85 percent of the patients had a murmur of pulmonary regurgitation. Because the cardiac catheterization data could not be evaluated for pulmonary regurgitation even qualitatively (very few had a main pulmonary arterial angiogram), we did not include pulmonary regurgitation in our analysis. Of the 31 patients with ventricular arrhythmia, 22 had cardiac catheterization.

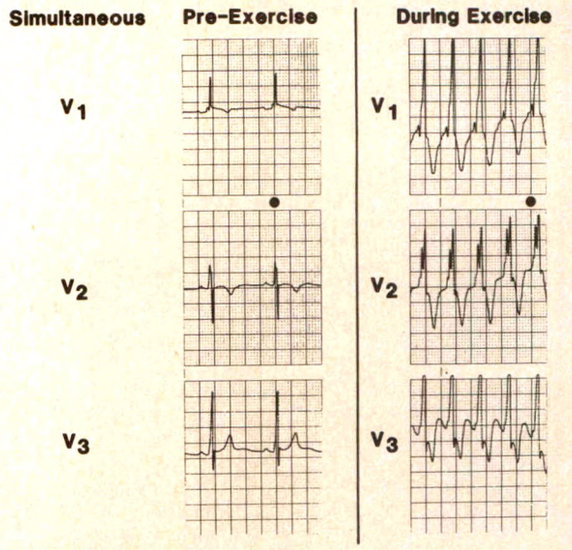


FIGURE 4. Exercise electrocardiogram of a 13 year old boy, 7 years after repair of tetralogy of Fallot. In the preexercise period, with a heart rate of 73 beats/min, the QRS duration is 0.08 second with increased anterior forces but without terminal conduction delay. During exercise testing, with a heart rate of 150 beats/min, the QRS duration increases to 0.14 second with a configuration of complete right bundle branch block.

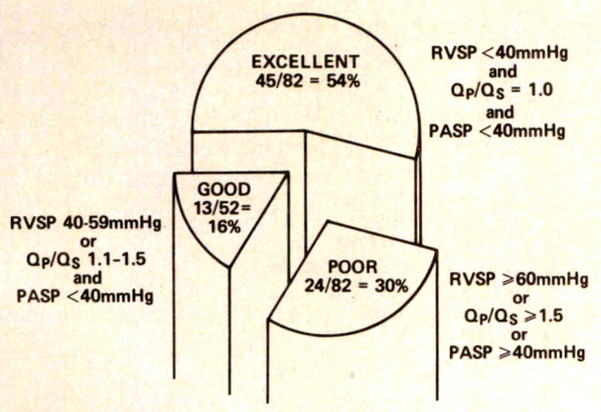


FIGURE 5. Hemodynamic results in 82 of the 104 patients who underwent postoperative cardiac catheterization. The definitions of the terms "excellent", "good" and "poor" hemodynamic result are shown in the figure. PASP = pulmonary arterial systolic pressure; Qp/Qs = pulmonary to systemic flow ratio; RVSP = right ventricular systolic pressure.

Relations Among Variables

Age and ventricular arrhythmia: When we compared those who had ventricular arrhythmia during the treadmill test with those who did not, we found that, although the age at intracardiac repair was similar in the two groups, those with ventricular arrhythmia were significantly older at the time of the test and were studied significantly longer after operation (Table I).

TABLE I

Age Versus Ventricular Arrhythmias During Treadmill Testing

	Ventricular Arrhythmias on Treadmill Test (n = 31)	No Ventricular Arrhythmias on Treadmill Test (n = 73)	p
Age at repair of TOF (yr)	7.3 ± 6.4*	6.6 ± 5.0	NS
Age at treadmill test (yr)	16.2 ± 1.1	12.8 ± 0.6	<0.01
Years postoperative at treadmill test	8.6 ± 1.0	6.4 ± 0.6	<0.05

* Standard error of the mean.
NS = not significant; p = probability; TOF = tetralogy of Fallot.

TABLE II

Electrocardiographic and Hemodynamic Data

	Pressures*			
	RVSP ≥60 mm Hg	RVED ≥8 mm Hg	PASP ≥40 mm Hg	Mean Qp/Qs Ratio
Routine electrocardiography	53	47	20	0.0
Ventricular arrhythmia present (15 patients)				
Ventricular arrhythmia absent (67 patients)	27	29	9	0.13
p	<0.05	NS	NS	NS
Treadmill testing	50	40	12	0.12
Ventricular arrhythmia present (22 patients)				
Ventricular arrhythmia absent (60 patients)	16	23	11	0.05
p	<0.001	<0.001	NS	NS

* Data are presented as percent of electrocardiographic group; for example, 53 percent of the 15 patients with ventricular arrhythmia on routine electrocardiography had a right ventricular systolic pressure of 60 mm Hg or more.

n = number; NS = not significant; p = probability; PASP = pulmonary arterial systolic pressure; Qp/Qs = pulmonary to systemic flow ratio; RVED = right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure.

Occurrence of ventricular arrhythmia and hemodynamics: Fifteen patients who had ventricular arrhythmia detected on the routine electrocardiogram at rest underwent cardiac catheterization. In eight (53 percent), the right ventricular systolic pressure was 60 mm Hg or greater. In 18 of 67 (27 percent) who had no arrhythmia on routine electrocardiography and who had undergone cardiac catheterization, the right ventricular systolic pressure was 60 mm Hg or more (Table II). Therefore almost twice as many patients with as those without premature ventricular complexes on electrocardiography at rest had an elevated right ventricular systolic pressure ($p < 0.05$). There was no other significant relation found in comparing the right ventricular end-diastolic pressure, pulmonary arterial systolic pressure or pulmonary to systemic flow ratio between patients with and without ventricular arrhythmia on routine electrocardiography. However, significantly more patients with than without ventricular arrhythmia during treadmill testing had an elevated right ventricular systolic pressure and more of the former group had a higher right ventricular end-diastolic pressure (Table II). Again, the pulmonary arterial systolic pressure and pulmonary to systemic flow ratio in these two groups were not different.

Timing of ventricular arrhythmia and hemodynamic status: Among the 31 patients who had ventricular arrhythmia at some time during the treadmill test, 15 had ventricular arrhythmia during exercise itself (Fig. 2) and 16 had ventricular arrhythmia either before or after exercise, but not while exercising (Table III). Thirteen from each group underwent cardiac catheterization and there was no significant difference in the hemodynamic status. There was also no difference between the hemodynamic status of the six patients who had ventricular arrhythmia only during (not before or after) exercise and that of the five patients who had ventricular arrhythmia before and after but not during exercise.

Form of ventricular arrhythmias and hemodynamics: Complex ventricular arrhythmias (multiform premature ventricular complexes, paired premature complexes or ventricular tachycardia) detected on the treadmill test were generally associated with an elevated right ventricular systolic pressure (Table IV). Almost all patients with complex arrhythmias had elevated right ventricular systolic pressure compared with approximately half of those with single, uniform premature ventricular complexes. The two patients who had multiform premature ventricular complexes on routine

TABLE III

Timing of Ventricular Arrhythmia and Hemodynamic Results

	RVSP ≥60 mm Hg	RVED ≥8 mm Hg
Ventricular arrhythmia during exercise	7/13 (54%)	8/13 (62%)
Ventricular arrhythmia before or after exercise	6/13 (46%)	7/12 (58%)

p = NS.

Abbreviations as in Table II.

TABLE IV

Form of Ventricular Arrhythmia and Hemodynamic Results

	RVSP ≥60 mm Hg
Uniform, single PVCs	7/16 (44%)
Multiform, single PVCs	3/4 (75%)
Paired PVCs	4/4 (100%)
Ventricular tachycardia	2/2 (100%)

PVCs = premature ventricular complexes; RVSP = right ventricular systolic pressure.

electrocardiography at rest also had them on treadmill testing, and in each the right ventricular systolic pressure was 60 mm Hg or more.

Follow-Up Period

The follow-up period ranged from 6 months to 5 years after the treadmill test with a mean of 2.1 years. Thus far, two patients have had cardiac arrest (neither episode was monitored), and one patient was successfully resuscitated. Each patient had abnormal hemodynamic findings and multiform premature ventricular complexes both on routine electrocardiography and immediately before treadmill testing. One patient exhibited ventricular tachycardia with exercise and had ventricular bigeminy in the recovery period. In the other patient, the arrhythmia disappeared completely with exercise and ventricular bigeminy occurred in the recovery period. Neither patient had left anterior hemiblock. After the test, both patients were treated with quinidine and had a cardiac arrest during treatment with this drug within 1 year of the treadmill test. Both had a serum concentration of quinidine in the therapeutic range within 3 months of the cardiac arrest.

Discussion

Prevalence and Prognosis of Ventricular Arrhythmias

Normal children: Ventricular arrhythmias can be either completely benign or lethal depending on the type of arrhythmia and the clinical situation. Single uniform premature ventricular complexes may be detected on routine electrocardiography in 2.4 percent of normal children.[4] In a long-term follow-up study of 17 children with a normal heart and premature ventricular complexes, Jacobsen et al.[4] demonstrated that the arrhythmia had disappeared in 9, a mean of 7 years later; the other 8 children continued to be asymptomatic. The response of all these normal patients with premature ventricular complexes at rest was complete suppression of the arrhythmia with exercise. Despite the stated lack of reproducibility of exercise testing in adults, exercise testing in children has been shown to be reproducible and a valuable provocative test for arrhythmias.[2,5–10] In normal children, single uniform premature ventricular complexes appear to be rare and benign.[4,10] Additional data on children with a normal heart and accelerated ventricular rhythm or ventricular tachycardia have shown that, in general, these arrhythmias are also well tolerated in children.[11–15]

Children after intracardiac repair: In children with an abnormal heart, premature ventricular complexes are more common and more dangerous. In a previous study from our institution with a different patient population,[1] we found the prevalence rate of ventricular arrhythmia on routine electrocardiography at rest in patients after intracardiac repair to be approximately 10 percent. Of those with ventricular arrhythmia, 38 percent died suddenly 3 months to 10 years after operation. None of these patients had left anterior hemiblock. Although the late development of complete A-V block may be a cause for a small number of late deaths after repair of tetralogy of Fallot,[16,17] a more common antecedent factor of late death appears to be ventricular arrhythmia.[18–21]

In this study, we found that 30 percent of patients had ventricular arrhythmia during treadmill exercise testing. This finding is in agreement with the 23 percent reported by James et al.[2] in patients after repair of tetralogy of Fallot. In contrast to the findings in children with a normal heart, ventricular arrhythmia in our patients occurred at various times during the test and suppression of premature complexes by exercise was not the typical response. Because such complexes were completely suppressed with exercise in one patient who later died suddenly, we also conclude that such suppression in patients with an abnormal heart is not necessarily associated with a benign outcome.

Type of ventricular arrhythmia at rest and during exercise: The implications of the occurrence of ventricular arrhythmias during exercise testing in a patient after repair of tetralogy of Fallot are uncertain. Two of our 31 patients with such arrhythmia during treadmill testing died suddenly. Both patients had multiform premature ventricular complexes on routine electrocardiography as well as during treadmill testing. There were no deaths among the 21 patients who had ventricular arrhythmia on treadmill testing only. Similarly, in the patients described by Winkler et al.[6] with complete A-V block and ventricular arrhythmias, those who later died had either ventricular arrhythmia on electrocardiography at rest or a complex arrhythmia (multiform premature ventricular complexes, couplets or ventricular tachycardia) on exercise testing. Therefore, it is apparent that among patients with an abnormal heart, those with any type of ventricular arrhythmia detected on routine electrocardiography at rest may have a poor prognosis. Our patients with uniform premature ventricular complexes found only during exercise testing do not appear to be at increased risk of death. Our information extends only for a mean of 2 years after treadmill testing and only further follow-up study will determine the outcome for patients with uniform premature complexes.

Other Prognostic Variables

Hemodynamics and ventricular arrhythmias: Our previous studies indicated a relation between the presence of premature ventricular complexes on electrocardiography at rest and elevated right ventricular pressure.[8] The results of our study confirm the association between abnormal hemodynamic findings and ventricular arrhythmia. However, because not all of the patients in our study with ventricular arrhythmia had abnormal hemodynamic findings, the finding of such arrhythmia is not an absolute predictor of a poor hemodynamic result.

Age and ventricular arrhythmia: We also found a significantly increased prevalence of ventricular arrhythmia on treadmill testing in older patients who were also studied at the longest interval after operation. In

normal adult volunteers, there is also an increase in prevalence of ventricular arrhythmia with increasing age.[22] It is possible that the larger prevalence of ventricular arrhythmia with age in our patients is simply due to a larger prevalence of "naturally occurring" ventricular arrhythmia. However, it is also possible that the longer a patient lives with a right ventriculotomy, residual patchy fibrosis and hypertrophy, the more likely he is to have ventricular arrhythmia.

Conclusions and Recommendations

1. Exercise testing is a more sensitive method for detecting ventricular arrhythmias than is routine electrocardiography and therefore is recommended for all patients who have had repair of tetralogy of Fallot.

2. Residual hemodynamic abnormality is generally associated with the presence of ventricular arrhythmia both on routine electrocardiography and with exercise testing. However, this association is not sufficiently predictive in an individual patient to permit avoidance of routine postoperative cardiac catheterization.

3. Although in children with a normal heart the characteristic response to exercise is suppression of ventricular arrhythmia, this is not the characteristic, nor necessarily the benign response in patients with an abnormal heart. Therefore, the finding of ventricular arrhythmia during an exercise test should be given equal weight whether the arrhythmia is detected in the preexercise, exercise or postexercise recovery electrocardiogram.

4. Complex ventricular arrhythmias (multiform or paired premature ventricular complexes, ventricular tachycardia) are highly associated with abnormal hemodynamic findings and sudden death. Antiarrhythmic treatment is therefore recommended for all patients with a complex arrhythmia, whether the arrhythmia is found on routine electrocardiography or provoked by exercise testing.

5. Ventricular arrhythmia may be a late developing phenomenon. Exercise testing every 2 to 3 years is therefore recommended for all patients.

Treatment: After intracardiac repair of tetralogy of Fallot, the prognosis for patients with complex ventricular arrhythmia or uniform premature ventricular complexes with elevated right ventricular systolic pressure is clearly poor, regardless of the conditions under which the arrhythmia occurred. Therefore, all these patients should be treated with antiarrhythmic medication. The significance of single uniform premature ventricular complexes in patients with a good hemodynamic result, whether detected on routine electrocardiography or during exercise testing, is unsettled. We consider treatment with a relatively benign drug such as phenytoin[23] to be superior to the possible consequences of ventricular tachycardia and sudden death. We recognize that this is an aggressive treatment policy for patients with postoperative arrhythmia and that other institutions may choose to adopt a different policy. If different treatment strategies are followed, then a comparison of the results should yield the optimal management plan for these patients.

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Dual Atrioventricular Nodal Pathways: A Benign Finding in Arrhythmia-Free Children With Heart Disease

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The incidence and significance of dual atrioventricular (A-V) nodal pathways are described in 78 children with associated congenital or acquired heart disease. None of these patients had clinical or electrocardiographic evidence of arrhythmia. Dual A-V nodal pathways were observed in 35 percent of the preoperative group and in 33 percent of the postoperative group. Despite this substrate for A-V nodal reentry, supraventricular tachycardia was neither induced during electrophysiologic evaluation nor did it develop clinically over a follow-up period of 1 month to 15 years. It is concluded that dual A-V nodal pathways are common and may be a benign finding in arrhythmia-free children with heart disease.

Moe et al.[1] provided evidence in animals of dual atrioventricular (A-V) nodal conduction pathways when they demonstrated an abrupt increase in the A-V conduction time when the atrial coupling interval was reduced. This resulted in discontinuous A-V conduction curves and implied the presence of parallel A-V conduction pathways with different electrophysiologic properties. Discontinuous A-V nodal conduction curves (A_1-A_2 and H_1-H_2) suggestive of the presence of dual A-V nodal pathways have been found in patients without supraventricular tachycardia[2,3] and have been demonstrated as a common mechanism for supraventricular tachycardia in adults and children.[2–10] Denes et al.[2] reported a 10 percent incidence rate of dual A-V nodal pathways in a mixed group of adults, most of whom had disease of the conduction system, whereas Thapar and Gillette[3] reported an overall incidence rate of 46 percent in a group of children, most of whom were evaluated because of arrhythmias. This report describes the incidence of dual A-V nodal pathways in 78 preoperative and postoperative children with cardiac defects in whom there was no clinical or electrocardiographic evidence of arrhythmias; they were found in 35 percent of the preoperative group and 33 percent of the postoperative group. Our observations indicate that dual A-V nodal pathways are common in arrhythmia-free children with heart disease and probably represent functional properties of the human A-V node.

Methods

Patients: Diagnostic cardiac catheterization and electrophysiologic studies were performed in 78 consecutive patients. The patients were classified into two groups. Group I consisted of 51 preoperative patients with the following heart defects: secundum atrial septal defect (10), ventricular septal defect (11), coarctation of the aorta (3), rheumatic heart disease (2), endocardial cushion defect (6), pulmonary valve stenosis (10), aortic valve stenosis (2), tetralogy of Fallot (2), corrected transposition of the great vessels (1), primary pulmonary hypertension (1), congenital mitral insufficiency (1) and myocarditis (1). One patient had a normal heart. The patients' ages ranged between 10 months and 18 years. Group II consisted of 27 patients with repaired cardiac defects: tetralogy of Fallot (17), ventricular septal defect (3), endocardial cushion defect (3), transposition of the great vessels (1), subvalvular aortic stenosis (2) and double

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outlet right ventricle (1). The patients' ages ranged between 2 and 18 years. The electrocardiograms in both groups revealed normal P-R intervals and no arrhythmias.

Electrophysiologic studies: The 78 patients were premedicated with combinations of Demerol®, Phenergan®, Thorazine® and Nembutal® (49); Demerol, Phenergan and Thorazine (26); Demerol and Nembutal (2); and general anesthesia (1). The electrophysiologic studies were conducted after completion of cardiac catheterization. A tripolar catheter was introduced percutaneously through the right femoral vein and positioned across the tricuspid valve for recording of the low septal right atrial and His bundle electrograms.[11] A second

TABLE I

Electrocardiographic and Electrophysiologic Data on 27 Children With Heart Defects and Dual A-V Nodal Pathways

Case	Sex & Age (yr)	Clinical Diagnosis	P-R	QRS	QRS Axis	Fast Pathway ERP/FRP	Slow Pathway ERP/FRP
			Group I (preoperative)				
1	F13	Rheumatic MI	136	75	+50	S = AR/<275; P = 240/270	S — P = AR/AR
2	M5	PS, rubella syndrome + PDA	151	70	+45	S = 280/380; P = 270/<360	S = AR/AR; P—
3	F8	ASD(2°)	113	85	+75	S =*; P = 240/<330	S =*; P = AR/AR
4	M14	ASD(2°)	160	75	+120	S = 330/585; P = 310/480	S = 280/660; P—
5	M5 6/12	AS	158	60	+90	S = 300/405; P = 310/395	S = 250/470; P = 240/465
6	F3	VSD	159	70	+80	S = 220/365; P =*	S = NR/NR; P =*
7	F10	Syncope, normal heart	169	65	+60	S = 280/430; P = NR/NR	S = NR/NR; P—
8	M16	Coarctation of aorta	125	85	+60	S = NR/NR; P = 320/425	S—; P = AR/AR
9	M1	VSD	70	135	+80	S = 260/315; P = NR/NR	S = <215/350; P—
10	F5	VSD	60	120	+60	S = 340/440; P = 340/415	S—; P = 300/430
11	F5	PS	95	140	+100	S = AR/AR; P = 270/360	S—; P = AR/AR
12	M4 6/12	ASD(2°)	80	141	+60	S = 250/400; P = 250/400	S = AR/AR; P = AR/AR
13	F5 6/12	Corrected TGV, VSD	85	166	+30	S = AR/AR; P = 220/340	S—; P = AR/AR
14	M7 6/12	PS, PPS	80	163	+90	S = 280/450; P = 300/440	S = AR/AR; P = 280/410
15	M4 1/12	Primary pulmonary hypertension	100	136	+135	S = 340/410; P = 260/410	S = <270/>410; P—
16	F17	Congenital mitral insufficiency	80	148	+75	S = AR/AR; P = 360/410	S—; P = 270/420
17	M17	PS	100	173	+110	S = 330/340; P = 350/425	S = AR/AR; P = 310/555
18	M4	VSD	75	139	+80	S = 260/355; P = 260/340	S = 240/395; P = <260/365
			Group II (postoperative)				
19	F9	To F (4)†	134	120	+90	S = 295/350; P = 310/370	S = AR/AR; P = AR/AR
20	F5	To F (3)†	190	190	+120	S = 310/400; P =*	S = AR/AR; P =*
21	F6	To F (2)†	149	100	+60	S = 455/520; P = 380/440	S = 300/665; P = 350/520
22	F5	To F (2)†	137	140	Indet.	S = 410/500; P = 450/510	S = 400/525; P—
23	M6	To F (2)†	160	120	Indet.	S = 570/610; P = 520/590	S = 450/600; P—
24	M6 6/12	ECD (4)†	157	75	−45	S = 260/330; P = 260/330	S = <260/<440; P = 250/420
25	F8 9/12	Subaortic stenosis (5)†	138	105	+75	S = 290/350; P = 290/355	S = AR/AR; P = AR/AR
26	M5 6/12	VSD (2 9/12)†	142	100	+90	S = 330/445; P = 330/425	S = AR/AR; P = AR/AR
27	M17	Subaortic stenosis (12)†	175	160	+10	S = 350/490; P = 350/490	S = 340/580; P = 340/550

* Refractory periods were not determined. † Numbers in parentheses indicate number of years after operation.

AR = limited by atrial refractoriness; AS = aortic stenosis; ASD(2°) = atrial septal defect (secundum); ECD = endocardial cushion defect; ERP = effective refractory period; FRP = functional refractory period; Indet. = indeterminate; MI = mitral insufficiency; NR = not reached; P = atrial paced cycle; P— = no dual pathways on paced rhythm; PDA = patent ductus arteriosus; PPS = peripheral pulmonic stenosis; PS = valvular pulmonic stenosis; S = sinus cycle; S— = no dual pathways on sinus rhythm; TGV = transposition of the great vessels; To F = tetralogy of Fallot; VSD = ventricular septal defect.

tripolar or tetrapolar catheter was introduced through the same femoral vein and positioned in the high right atrium for stimulation and for recording the high right atrial electrogram.

Surface electrocardiographic leads I, II, III or I, II and V_1 and intracardiac electrograms were recorded simultaneously on a multichannel photographic recorder (Electronics for Medicine DR-12, White Plains, New York) with a paper speed of 100 mm/s and filter settings of 40 to 500 hertz. Stimuli were delivered by a programmable digital stimulator (Medtronics model 5325 programmable stimulator) with a strength of twice diastolic threshold and a duration of 2 ms.

Rapid atrial pacing and programmed atrial extrastimulation were performed in all patients. The atrial and atrioventricular (A-V) nodal refractory periods were determined utilizing the atrial extrastimulus technique.[12] Coupling of an atrial extrastimulus to both sinus and atrial paced cycle lengths was performed in 61 of the 78 patients; coupling of the extrastimulus to sinus cycle length only or to an atrial paced cycle length only was performed in 14 and 3 patients, respectively.

Ventricular extrastimulation studies were performed in 54 patients and in the majority the extrastimulus was coupled to the sinus rhythm.

The atrial or ventricular test stimulus (S_2) was introduced after every eighth spontaneous or driven beat (S_1). The coupling interval was decreased by 10 to 20 ms decrements during both atrial and ventricular extrastimulation.

Definitions: HRA_1, A_1, H_1 and V_1 refer, respectively, to the high right atrial, low septal right atrial, His bundle and ventricular electrograms of spontaneous sinus or driven beats. HRA_2, A_2, H_2 and V_2 refer to the respective responses to the extrastimulus (S_2). Refractory periods and A-V conduction intervals were defined and measured as described by Denes et al.[13] and Castellanos et al.,[14] respectively.

The diagnosis of dual A-V nodal pathways was based on the induction of discontinuous A-V nodal conduction curves (A_1-A_2 and H_1-H_2) with programmed atrial extrastimulation.[2,6] The curve to the right of the discontinuity reflected fast A-V nodal pathway conduction, and to the left slow A-V nodal pathway conduction. The effective refractory period of the fast A-V nodal pathway was the longest A_1-A_2 interval that failed to conduct through the fast A-V nodal pathway, and its functional refractory period was the shortest H_1-H_2 interval on the fast A-V nodal pathway curve. The effective refractory period of the slow A-V nodal pathway was the longest A_1-A_2 interval that was not conducted through the slow A-V nodal pathway, and its functional refractory period was the shortest H_1-H_2 interval on the slow A-V nodal pathway curve.

A-V nodal reentry was diagnosed by the occurrence of atrial echoes with a low to high atrial activation sequence. The echo zone was defined as the zone within which atrial extrastimuli induced atrial echoes.[15–17] The critical A-H interval was the shortest A_2-H_2 interval inducing an atrial echo.[18]

Results

Dual A-V nodal pathways were demonstrated in 27 (35 percent) of the 78 patients—18 (35 percent) of the 51 in the preoperative group and 9 (33 percent) of the 27 in the postoperative group. Of 27 patients who had dual atrioventricular (A-V) nodal pathways 24 were studied with the atrial extrastimulus coupled to both sinus and paced rhythms. In 11 of these 24 patients dual A-V nodal pathways were documented during coupling of the atrial extrastimulus to both sinus and paced atrial rhythms: in 7 during sinus rhythm only and in 6 during paced rhythm only.

In 20 of the 27 patients with dual A-V nodal pathways, ventricular extrastimulation was performed. Ventriculoatrial (V-A) conduction was present in 10 patients, an incidence rate of 50 percent. The incidence rate of V-A conduction in patients without dual A-V nodal pathways was 49 percent.

The effective and functional refractory periods of the fast A-V nodal pathway ranged between 220 and 570 and 270 and 610 ms, respectively, whereas the effective and functional refractory periods of the slow A-V nodal pathway ranged between 240 and 450 and 350 and 665 ms, respectively (Table I). Accurate measurement of the refractory periods of the slow A-V nodal pathway was limited by atrial refractoriness in 12 patients. The effective and functional refractory periods of the fast A-V nodal pathway in the preoperative group were 287 ± 42 and 398 ± 61 ms, respectively. The effective and functional refractory periods of the fast A-V nodal pathway in the postoperative group was 345 ± 80 and

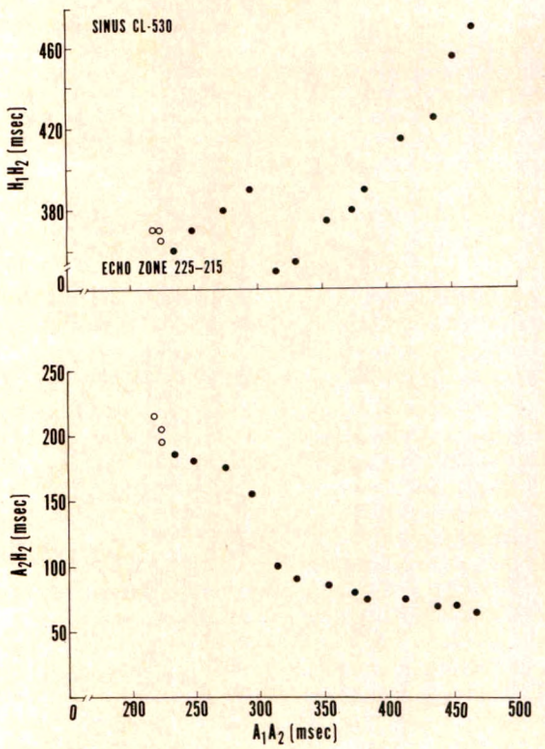


FIGURE 1. Patient 19. A-V conduction curves (A_1A_2 and H_1H_2; A_1A_2 and A_2H_2) during atrial extrastimulation coupled to sinus rhythm. The average sinus cycle length (CL) is 530 ms. Note discontinuity due to a sudden increase in atrioventricular (A-V) nodal conduction time (A_2H_2) at a coupling interval of 295 ms. In this and subsequent figures **closed circles** represent responses without atrial echoes; **open circles** represent responses with atrial echoes. The effective and functional refractory periods of the fast pathway were 295 and 350 ms, respectively. The effective and functional refractory periods of the slow pathway were limited by atrial refractoriness. The echo zoned ranged between 225 and 215 ms. Sustained supraventricular tachycardia was not induced.

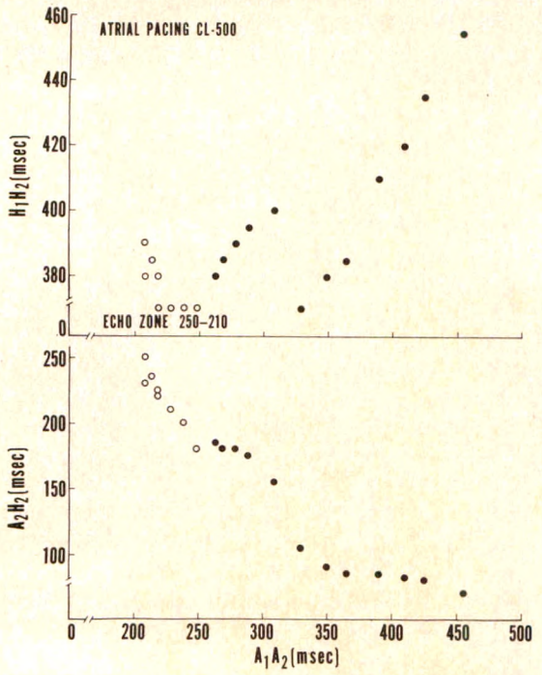


FIGURE 2. Patient 19. A-V conduction curves (A_1A_2 and H_1H_2; A_1A_2 and A_2H_2) during atrial extrastimulation coupled to a high right atrial pacing cycle length of 500 ms. Note discontinuity due to a sudden increase in A-V nodal conduction time (A_2H_2) at a coupling interval (A_1A_2) of 310 ms. The effective and functional refractory periods of the fast pathway were 310 and 370 ms, respectively. The effective and functional refractory periods of the slow pathway were limited by atrial refractoriness. The echo zone ranged between 250 and 210 ms. Sustained supraventricular tachycardia was not induced.

427 ± 83 ms, respectively. Slow A-V nodal pathway refractory periods were limited by atrial refractoriness in the majority of patients.

Representative cases: Figure 1 demonstrates the induction of discontinuous A-V nodal conduction curves (A_1-A_2 and H_1-H_2; A_1-A_2 and A_2-H_2) in Patient 19 (Table I) during atrial extrastimulation coupled to sinus rhythm. The average sinus cycle length was 530 ms. At a coupling interval (A_1-A_2) of 295 ms there was a sudden prolongation in the A_2-H_2 interval of 55 ms resulting in discontinuous A-V nodal conduction curves. The echo zone could be defined between coupling intervals (A_1-A_2) of 225 and 215 ms. Sustained A-V nodal reentry was not induced. The effective and functional refractory periods of the fast A-V nodal pathway were 295 and 350 ms, respectively. The measurement of the refractory periods of the slow A-V nodal pathway was limited by atrial refractoriness. The echo zone was narrower during atrial extrastimulation coupled to sinus rhythm than during that coupled to paced rhythm (Fig. 2).

Figure 2 demonstrates the induction of discontinuous A-V nodal conduction curves (A_1-A_2 and H_1-H_2; A_1-A_2 and A_2-H_2) in this patient during atrial pacing. The paced atrial cycle length (S_1-S_2) is 500 ms. At a coupling interval (A_1-A_2) of 310 ms there was sudden prolongation in the A_2-H_2 interval of 50 ms resulting in discontinuous A-V nodal conduction curves. The echo zone could be defined between coupling intervals (A_1-A_2) of 250 and 210 ms. The effective and functional refractory periods of the fast A-V nodal pathway were 310 and 370 ms, respectively. The measurement of the refractory periods of the slow A-V nodal pathway was also limited by atrial refractoriness. This was the only patient in whom atrial echoes were elicited. Sustained A-V nodal reentrant tachycardia could not be elicited in any patient.

Figure 3 demonstrates the electrophysiologic tracings from Patient 3 (Table I) during atrial extrastimulus coupled to a paced cycle length of 490 ms. Electrocardiographic leads I, II, III and His bundle electrograms are shown. In panel A, an atrial premature beat at a coupling interval (A_1-A_2) of 250 ms results in an A_2-H_2 of 160 ms. In panel B, an atrial premature beat at a coupling interval (A_1-A_2) of 240 ms prolongs the A-H interval to 230 ms, resulting in discontinuous A-V nodal conduction curves.

The sudden increase or jump in A-V conduction time (A_2-H_2) resulting when conduction failed in the fast A-V nodal pathway and shifted to the slow A-V nodal pathway ranged between 40 and 185 ms in the entire group.

Discussion

Mechanism of supraventricular tachycardia: Atrioventricular nodal reentry is a common cause of supraventricular tachycardia in adults[6,19,20] and children[3,8,10] and electrophysiologic studies have confirmed that dual atrioventricular (A-V) nodal pathways are a frequent underlying mechanism for supraventricular tachycardia.[2,3,8–10] The slow-fast form of A-V nodal reentrant tachycardia involves a slow A-V nodal pathway for anterograde conduction and a fast A-V nodal pathway for retrograde conduction.[19,20] However, the fast-slow form utilizes a fast A-V nodal pathway for anterograde conduction whereas retrograde conduction occurs through a slow A-V nodal pathway.[7,19,20] Both forms of A-V nodal reentry have been demonstrated in children.[3,7,8] Studies in adults have primarily involved patients with conduction disease. Denes et al.[9] found a 10 percent incidence rate (41 of 397 patients) of dual A-V nodal pathways in a group of such patients, but 16 (39 percent) of the 41 patients had no history of palpitations or supraventricular tachycardia. This benignity appears to apply to pediatric patients as well. Therefore, dual A-V nodal pathways are common in both adults and children.

Incidence of dual A-V nodal pathways: Both DuBrow et al.[10] and Thapar and Gillette[3] have reported the presence of dual A-V nodal pathways in arrhythmia-free children. Of 61 children studied by Thapar and Gillette[3] the majority had some rhythm disorder, but 17 children with a cardiac defect without arrhythmia demonstrated a 29 percent incidence of dual A-V nodal pathway conduction before surgery. This is in agreement with our findings of a 35 percent incidence rate in an unselected group of preoperative and postoperative patients (35 percent in the former group alone and 33 percent in the latter group alone). This high incidence rate of dual A-V nodal pathways may be related to the significantly shorter atrial and A-V nodal refractory periods in children.[21,22] It has been suggested[3,23,24] that these electrophysiologic changes cor-

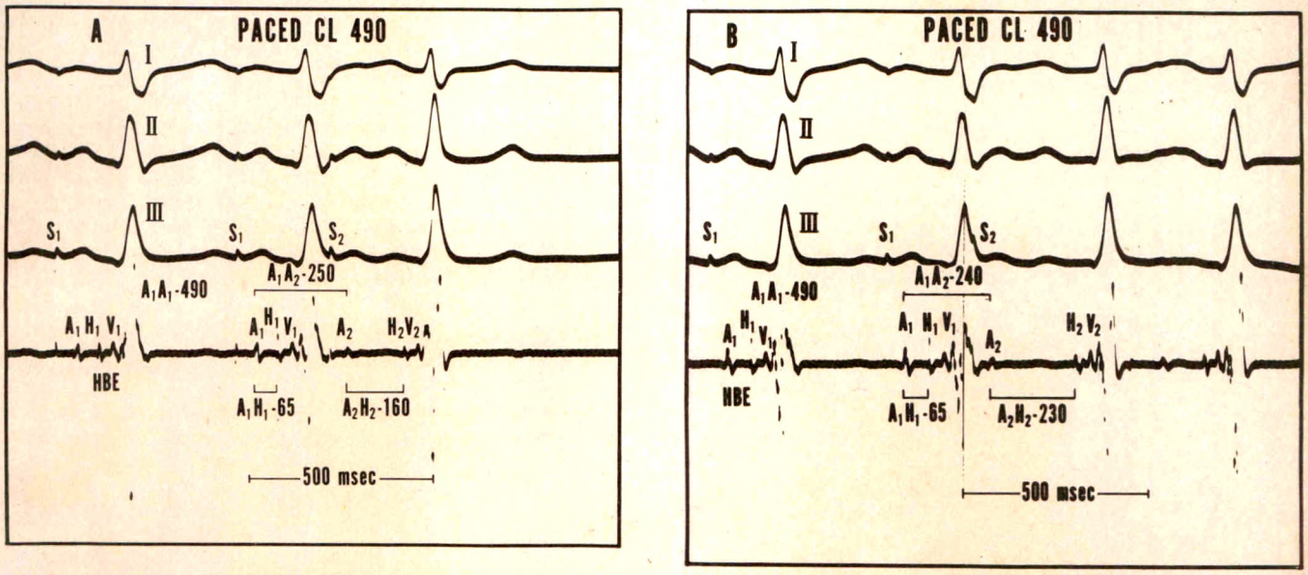


FIGURE 3. Patient 3. His bundle electrogram during atrial extrastimulation coupled to a paced cycle length (CL) of 490 ms. Electrocardiographic leads I, II and III and His bundle electrogram (HBE) are shown. S_1 and S_2 represent atrial pacing and premature stimuli, respectively. A_1, H_1 and V_1 represent the low right atrium, His bundle and ventricular electrogram during pacing. A_2, H_2 and V_2 represent the responses to a premature atrial extrastimulus (S_2). **A,** at a coupling interval (A_1A_2) of 250 ms the A_2H_2 interval is 160 ms. **B,** at a coupling interval (A_1A_2) of 240 ms the A_2H_2 interval prolongs to 230 ms resulting in discontinuous A-V nodal conduction curves.

relate with maturational histologic changes. In addition, Sapire et al.[25] have demonstrated that meperidine (Demerol), promethazine (Phenergan) and chlorpromazine (Thorazine) shorten A-V nodal refractory periods. These medications, by their shortening effect on refractory periods, may unmask the presence of dual A-V nodal pathways by allowing conduction at shorter coupling intervals when the slow A-V nodal pathway is utilized for conduction after the fast A-V nodal pathway refractory period has been reached.

In general, atrial paced rhythm decreases atrial refractoriness and prolongs the refractory periods of the fast A-V pathway by shortening the atrial cycle length.[13] Therefore, dual A-V nodal pathway conduction is expected to be observed more frequently during atrial paced rhythm than during sinus rhythm. The finding that such conduction occurred during sinus rhythm but not during atrial paced rhythm in seven of our patients was unusual. In four patients (Cases 2, 4, 15 and 23) we could attribute this finding to paradoxical shortening of the effective refractory period of the fast A-V nodal pathway induced by atrial pacing. This would prevent exposure of dual A-V nodal pathways because the fast A-V nodal pathway is used at both long and short coupling intervals. This shortening of the refractory period of the fast A-V nodal pathway with atrial pacing is the expected response of atrial and His-Purkinje tissue and is unusual in A-V nodal tissue.[13]

Incidence of supraventricular tachycardia: None of our patients had sustained A-V nodal reentrant tachycardia during electrophysiologic studies and only one patient (Case 19) had atrial echoes. This small incidence of echoes is probably a reliable finding because more than half of our patients had high right atrial recordings, and the atrial electrograms were clearly discernible. The failure to induce sustained supraventricular tachycardia may be explained by this absence of atrial echoes.[9]

Supraventricular tachycardia has not been observed clinically in any of our patients during a follow-up period of 1 month to 15 years. Whether dual A-V nodal pathways will persist with maturation in an individual patient cannot be predicted from our data because only two children have had sequential electrophysiologic studies; both children demonstrated dual pathways before and 2 years after surgery. Although the substrate exists for A-V nodal reentry, the initiation of sustained supraventricular tachycardia depends on an interplay of many factors. These include the presence or absence of atrial or ventricular extrasystoles and alterations in the functional properties of each A-V nodal pathway in relation to age, cycle length, autonomic tone and medications. In our patients the interplay of these factors was not synchronized for reentrant tachycardia. Therefore, dual A-V nodal pathways are a common and frequently a benign electrophysiologic phenomenon in children and may represent normal functional characteristics of the human A-V node.

Acknowledgment

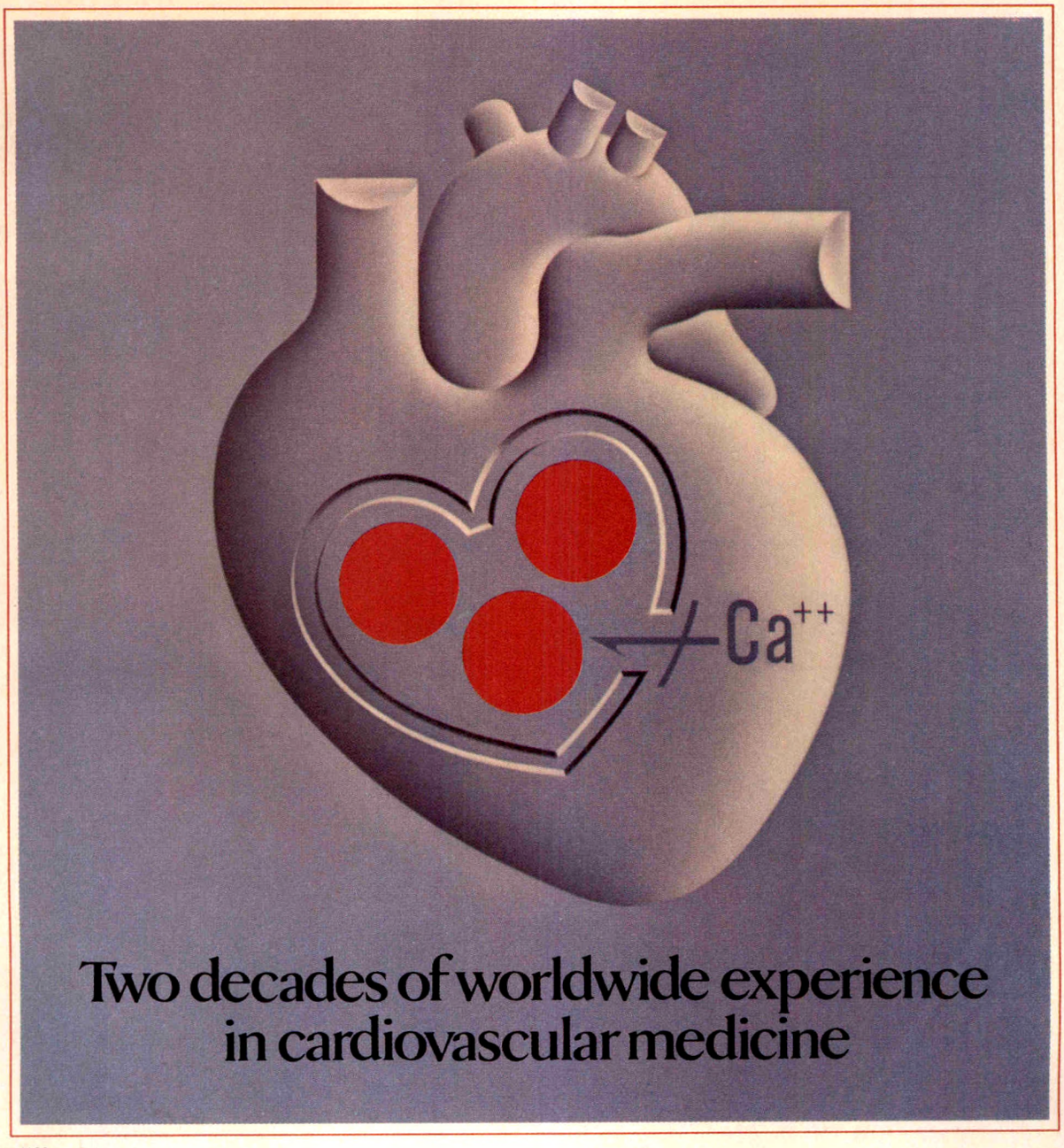
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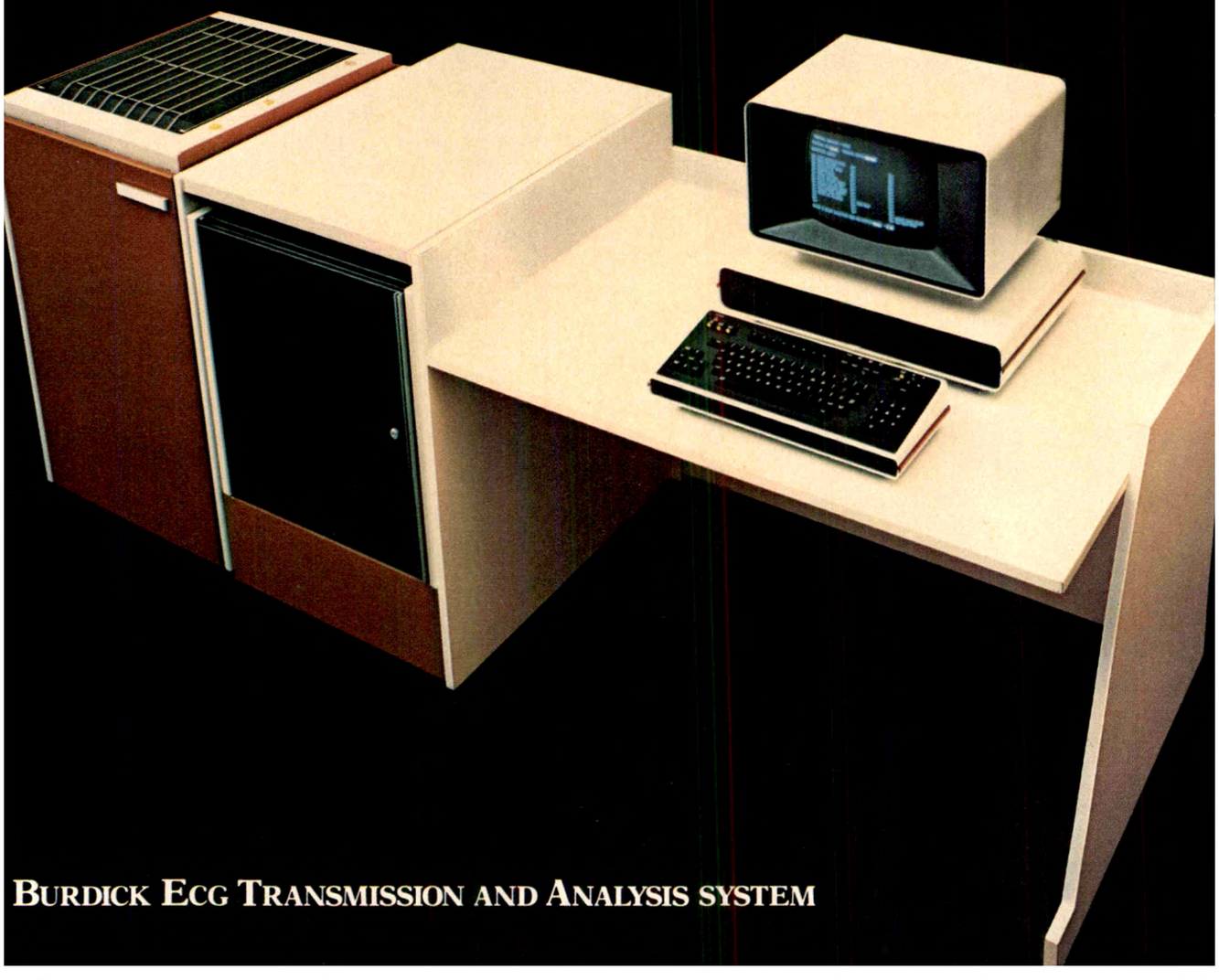


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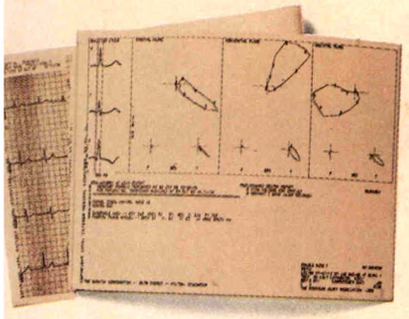
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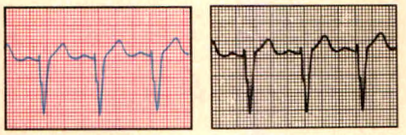
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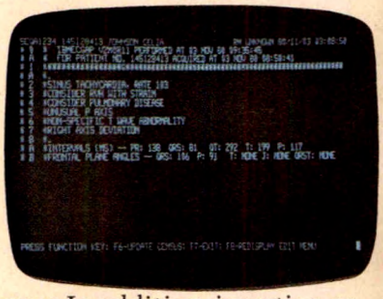
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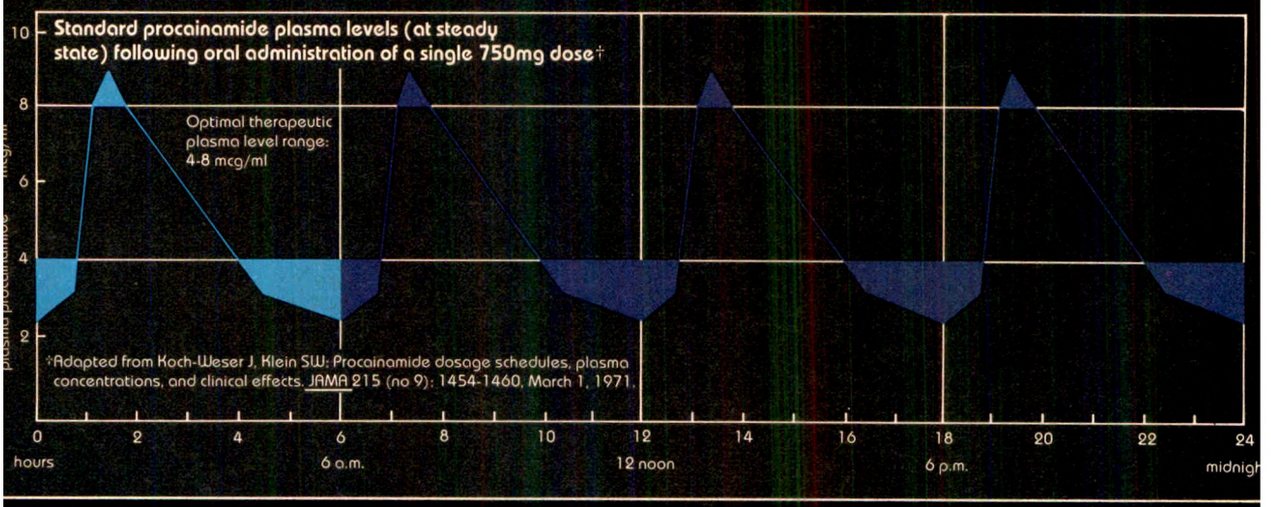
Procan™ SR

PROCAINAMIDE HYDROCHLORIDE TABLETS

therapeutic gap exists when
onventional oral procainamide therapy is administered
t greater than 3 hour intervals

Adequate blood levels maintained only 2/3 of the
me during a 6 hour dosing interval

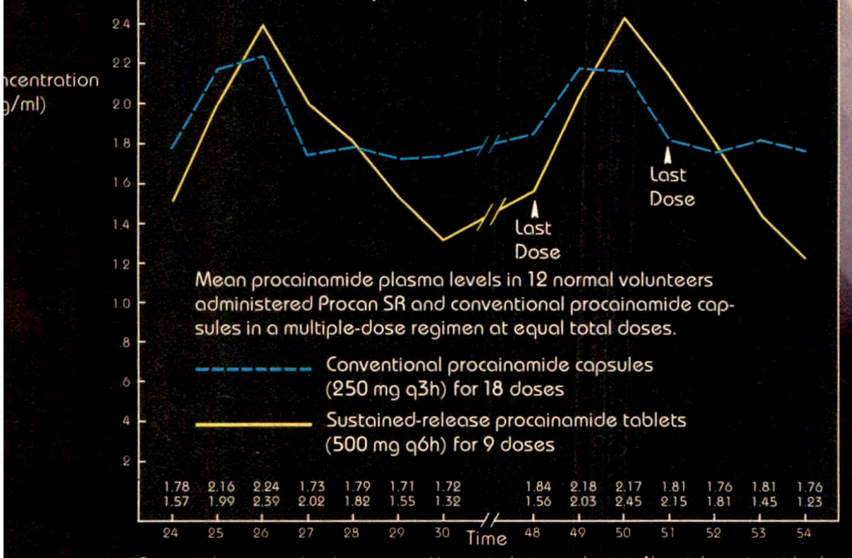
Patient control may be threatened



To avoid unacceptable fluctuations
the plasma levels of procainamide, the oral
reparation available at present has to be
iven at 3 h intervals [1]

ioequivalence of PROCAN SR o conventional rocainamide capsules emonstrated in ulti-dose study[2]

Procan SR q6h demonstrates bioequivalence* to short-acting formulation of oral procainamide q3h in multidose study after steady state is achieved[2]



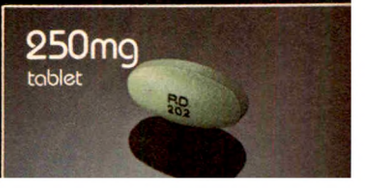
Mean procainamide plasma levels in 12 normal volunteers administered Procan SR and conventional procainamide capsules in a multiple-dose regimen at equal total doses.

- Conventional procainamide capsules (250 mg q3h) for 18 doses
- Sustained-release procainamide tablets (500 mg q6h) for 9 doses

*Bioequivalence was also demonstrated by equivalent steady-state N-acetylprocainamide plasma levels, by equivalent procainamide steady-state urinary excretion, and by equivalent total procainamide 0 to 96 hour urinary excretion (58.7% of procainamide doses were excreted in urine with PROCAN SR, compared with 60% for conventional procainamide capsules).

■ Formulated using a special wax matrix — permits slow dissolution

2 strengths for greater flexibility



or selected cardiac dysrhythmias

■ Cuts the dosing frequency of conventional oral procainamide therapy **in half**

Procan™ SR

(PROCAINAMIDE HYDROCHLORIDE TABLETS)

SUSTAINED RELEASE

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

DESCRIPTION

Procainamide hydrochloride is the amide analogue of procaine hydrochloride. Each tablet of Procan SR contains procainamide hydrochloride in a tablet matrix specially designed for the prolonged release of the drug in the gastrointestinal tract. Procan SR is available for oral administration as green, film-coated tablets containing 250 mg procainamide hydrochloride and as yellow, film-coated tablets containing 500 mg procainamide hydrochloride.

ACTION

Procainamide depresses the excitability of cardiac muscle to electrical stimulation, and slows conduction in the atrium, the bundle of His, and the ventricle. The refractory period of the atrium is considerably more prolonged than that of the ventricle. Contractility of the heart is usually not affected nor is cardiac output decreased to any extent unless myocardial damage exists. In the absence of any arrhythmia, the heart rate may occasionally be accelerated by conventional doses, suggesting that the drug possesses anticholinergic properties. Larger doses can induce atrioventricular block and ventricular extrasystoles which may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram; a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

The sustained-release characteristic of Procan SR tablets has been demonstrated in studies in human subjects. A multiple-dose study has shown equivalent steady-state plasma levels of Procan SR tablets given every six hours when compared with an equal total daily dose of Pronestyl® (procainamide hydrochloride capsules, E.R. Squibb and Sons) given every three hours.

Procainamide is less readily hydrolyzed than procaine, and plasma levels decline slowly — about 10 to 20% per hour for standard dosage forms of procainamide. The drug is excreted primarily in the urine, about 10% as free and conjugated p-aminobenzoic acid, and about 60% in the unchanged form. The fate of the remainder is unknown.

INDICATIONS

Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS

During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs'-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

ADVERSE REACTIONS

Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS). Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION

Procan SR tablets are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every three hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia — Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dosage of 50 mg/kg of body weight given at three hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia — Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows. An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dosage of 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED

N 0071-0202 Procan SR 250 mg. Each sustained-release tablet contains 250 mg procainamide hydrochloride. Available in bottles of 100 tablets.

N 0071-0204 Procan SR 500 mg. Each sustained-release, scored tablet contains 500 mg procainamide hydrochloride. Available in bottles of 100 tablets.

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Antianginal and Myocardial Metabolic Properties of Verapamil in Coronary Artery Disease

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Long Beach, California
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To determine the metabolic cost of administering an experimental calcium antagonist, verapamil, to patients with coronary artery disease, 12 such patients were studied at rest and during stress with atrial pacing before and after intravenous treatment with verapamil (bolus dose of 0.1 mg/kg body weight, followed by infusion at 0.005 mg/kg per min). The mean (±standard deviation) aortic pressure at rest (98 ± 22 mg Hg), coronary sinus blood flow (88 ± 17 ml/min) and myocardial oxygen consumption (10.7 ± 2.4 ml O_2/min) decreased to 88 ± 20 mm Hg ($p < 0.0004$), 77 ± 14 ml/min ($p < 0.03$) and 8.8 ± 2.5 ml O_2/min ($p < 0.01$), respectively, after administration of verapamil. With atrial pacing, these values were 105 ± 25 mm Hg, 151 ± 50 ml/min and 18.5 ± 6.4 ml O_2/min, respectively, before infusion of verapamil, and then decreased to 87 ± 14 mm Hg ($p < 0.006$), 107 ± 31 ml/min ($p < 0.0002$) and 13.3 ± 4.4 ml O_2/min ($p < 0.001$) during infusion. Angina occurred in all patients with atrial pacing before verapamil (threshold to pain: 93 ± 67 seconds). After verapamil, the threshold to pain in six patients increased to 191 ± 183 seconds; and no pain was experienced by the remaining six ($p < 0.0005$). Before administration of verapamil lactate extraction decreased from 24 ± 9 to 10 ± 11 percent ($p < 0.0002$) during atrial pacing, and 9 (75 percent) of the 12 patients exhibited electrocardiographic S-T segment depressions. After administration of verapamil lactate extraction normalized to 22 ± 9 percent during atrial pacing, and the electrocardiogram reverted to baseline in all but one patient. These findings indicate that verapamil decreases left ventricular myocardial metabolic demands, and concomitantly greatly increases the threshold to angina.

Verapamil, still an experimental drug in the United States, has multiple effects on the cardiovascular system. Because it is an organic calcium antagonist,[1,2] its actions are due to the selective blockade of the slow channel that carries the slow inward ionic current consisting of calcium (and probably sodium) ions.[3–6] These properties make verapamil an effective antiarrhythmic agent[7–11] and may eventually be used to reduce the size of an acute infarct.[12–16] However, fear persists that verapamil's intrinsic negative inotropic effects may preclude its use in patients with significant coronary artery disease because both verapamil[17,18] and ischemia[19,20] interfere with the movement of calcium ions to the contractile proteins of myocardial cells and could therefore in theory synergistically impede calcium transport, causing a profound depression of myocardial contractility.

Recent studies in our laboratory[21] have shown that the administration of verapamil to patients with coronary artery disease without congestive heart failure does not depress, but actually enhances total left ventricular performance. Furthermore, the drug is often capable of reducing the regional disorders of left ventricular wall motion.[21] However, the metabolic cost to patients of this improved performance—not only at rest but also during stress—is not known. This study was therefore undertaken to examine the changes in myocardial metabolism that might occur

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in patients with chronic coronary artery disease without heart failure after administration of verapamil, and to establish whether these changes differ substantially before and after stress induced by rapid atrial pacing. Moreover, this study was also designed to answer the critical question: Does verapamil protect patients with coronary artery disease from angina pectoris?

Methods

Study patients: Twelve men with significant coronary artery disease were selected for this study. Their clinical profile is presented in Table I. All gave informed consent and underwent routine diagnostic cardiac catheterization, which, in our laboratory, includes complete left and right hemodynamic evaluation, cardiac output determination with the indocyanine green indicator-dilution technique, selective left ventriculography and coronary arteriography. All patients had normal sinus rhythm; none had systemic hypertension, significant valve or congenital lesions or a history of congestive heart failure. Patients with clinically significant renal or hepatic failure, left bundle branch block, sinus bradycardia, systolic blood pressure below 90 mm Hg or recent myocardial infarction (within the last 3 months) were excluded from the study. No patient had to be excluded from the study because of adverse effects caused by verapamil, or because complete evaluation could not be performed for technical reasons.

Some patients had previously received one or more cardiovascular medications, but in each the administration of all drugs, with the exception of sublingual nitroglycerin, was discontinued at least 5 days before the study without any clinical evidence of deterioration of cardiac function or increase in chest pain. No patient had to take nitroglycerin in the 12 hours preceding cardiac catheterization although this drug was made available to all.

Study protocol: The study consisted of four phases: resting and atrial pacing phase before administration of verapamil, followed by another resting and pacing phase after administration of the drug, so that the entire third and fourth phases of the study were implemented during the infusion of verapamil. Measurements of coronary sinus blood flow and collection of blood samples were performed during each phase. For this purpose, a 7F double thermistor Wilton Webster coronary sinus thermodilution catheter was inserted into the coronary sinus. The design of this catheter allows continuous blood sampling from the coronary sinus and simultaneous atrial pacing from the same site. When connected to the Wilton Webster two channel Wheatstone bridge and a chart recorder, it accurately measures the coronary sinus blood flow with the thermodilution method;[22] values so obtained correlate well with direct measurements of coronary sinus blood flow with the electromagnetic flowmeter.[23,24] Arterial blood samples were collected through an 8F Cordis catheter positioned in the descending aorta. A third catheter (7F Cournand) was placed in the right atrium for constant atrial pressure monitoring because it has been shown that changing right atrial pressures may invalidate coronary sinus thermodilution blood flow measurements by causing the reflux of blood from the right atrium into the coronary sinus.[25] The exact location of the thermodilution catheter within the coronary sinus was established at the beginning of each study by cineangiography recorded on the videotape, and the catheter's stability was then continuously confirmed during the entire experiment by referring to the initial cine frames.

Arterial and coronary sinus blood determinations: Matched samples of the arterial and coronary sinus blood that were collected simultaneously and in duplicate during each phase were analyzed for the content of the following items: lactate, potassium, sodium, chloride, calcium, phosphate and blood gases. Lactate levels were determined with the Gilford computer-directed analyzer, and potassium, sodium, chloride, calcium and phosphate content with the Technicon Autoanalyzer. Blood gases were analyzed with the Corning automated blood gas system. Aortic (Ao) to coronary sinus (CS) ratios of potassium, sodium, calcium and phosphate were calculated for each matched pair of blood samples. The percent of lactate extraction was defined as

$$\% \text{ extraction} = \frac{\text{Lactate Ao} - \text{Lactate CS}}{\text{Lactate Ao}} \times 100.$$

A negative number indicates lactate production and therefore represents a shift from aerobic to anaerobic metabolism.[26]

Blood flow and myocardial oxygen determinations: Coronary sinus blood flow measurements were performed during continuous infusion of the indicator (5 percent dextrose in water at room temperature) with a Harvard infusion pump at 55 ml/min. Even though stable and reproducible values were normally obtained within 15 seconds after the infusion had been started, the infusion was continued for at least 1 min before coronary sinus blood flow determinations were made (to achieve optimal mixing and equilibration of blood and the indicator). Myocardial oxygen consumption (MVO_2) was calculated as the product of coronary sinus blood flow (CSBF) and arterial-coronary venous oxygen difference [MVO_2 = CSBF × (Ao − CS)$O_2\Delta$].

Atrial pacing protocol: An atrial pacing rate of 150 beats/min was achieved in almost all patients. In a few pa-

TABLE I

Clinical Profile of 12 Study Patients

Patients (n)	12
Mean age (±1 standard deviation) (yr)	55 ± 7
Stable angina	All
Positive treadmill stress test (≥1 mm S-T depression)	8 (67%)
Coronary obstruction (≥75%)	
1 vessel	0
2 vessel	2 (17%)
3 vessel	10 (83%)
Prior myocardial infarction	5 (42%)
Left ventricular asynergy	7 (58%)
History of congestive heart failure	None

SD = standard deviation.

TABLE II

Baseline Hemodynamic Values in 12 Study Patients (mean ± standard deviation)

LVEDP (mm Hg)	12 ± 4
Mean AP (mm Hg)	97 ± 17
Mean PAP (mm Hg)	17 ± 5
Mean PCWP (mm Hg)	8 ± 2
CI (liters/min per m^2)	2.8 ± 0.5
EDVI (ml/m^2)	117 ± 45
ESVI (ml/m^2)	53 ± 55
EF (%)	62 ± 24
VCF (circ/s)	0.94 ± 0.42

AP = arterial pressure; CI = cardiac index; circ = circumference; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LVEDP = left ventricular end-diastolic pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; VCF = mean velocity of circumferential fiber shortening.

tients a slightly slower pacing rate had to be used before and after administration of verapamil because of the occurrence of second degree atrioventricular (A-V) block (Mobitz type I). All patients were carefully instructed not to interpret the palpitations that are sometimes associated with atrial pacing as chest pain and were given a trial pacing run at maximal rates to familiarize them with the procedure. Atrial pacing during the actual test was continued for 5 minutes or until the onset of the patient's typical chest pain. As soon as either end point was reached, coronary sinus blood flow measurements and blood sample collections were performed, and atrial pacing was terminated immediately thereafter. The electrocardiogram (leads II and V_5) was carefully monitored throughout the study, and the extent of S-T segment depression was recorded on the chart recorder immediately before and after the termination of pacing.

Factors that influence coronary hemodynamics were monitored during each phase of the study. Specifically, aortic pressures and heart rate were recorded continuously. Coronary vascular resistance (CVR) was calculated as the ratio of mean aortic pressure to coronary sinus blood flow (CVR = mean Ao pressure/CSBF).[22]

Verapamil dosage: Verapamil (0.1 mg/kg) was given as a bolus dose intravenously over a 2 minute period; the intravenous verapamil infusion of 0.005 mg/kg per min was started with an Auto Syringe infusion pump immediately after the bolus injection and continued until all data were collected. The mean total dose of verapamil was 18.8 ± 3.6 mg, and the length of the infusion averaged 24 ± 5 minutes.

Ventriculography and coronary angiography: When left ventriculography and coronary cineangiography were performed before verapamil infusion, a predetermined time period was allowed to elapse before any given verapamil phase of the study was initiated. No tests were carried out during 45 minutes after ventriculography (to eliminate the pharmacologic effects of contrast medium on myocardial contractility[27,28]) and during 15 minutes after coronary cineangiography (to avoid the possible effects of transient reactive hyperemia on coronary flow or myocardial contractility[29,30]).

All coronary cineangiograms were of diagnostic technical quality. Significant coronary artery disease was considered present only when there was at least a 75 percent obstruction of luminal diameter of at least one of the three coronary arteries, and when this observation was confirmed by two independent observers. Ten (83 percent) of the 12 patients had triple vessel disease (Table I); a left anterior descending lesion was present in 11 (92 percent) patients.

Statistical analysis: All data were analyzed with the Student's *t* test for paired variables,[31] with the exception of pacing time to angina, which did not always have a definite end point (half of the patients had no pain after treatment with verapamil) and was therefore evaluated with the Wilcoxon signed rank test.[32] The mean values are always presented with ±1 standard deviation.

Results

Hemodynamics: The baseline hemodynamic values for all patients are given in Table II. This hemodynamic profile is characterized by normal pressures, normal cardiac index, normal left ventricular size in end-systole and end-diastole and normal indexes of contractility (ejection fraction and velocity of circumferential fiber shortening).

Figures 1 and 2 depict changes in myocardial and circulatory dynamics that occurred at rest and during

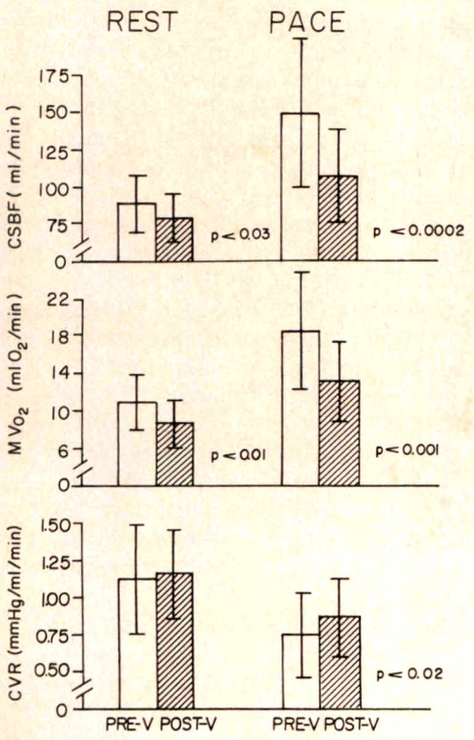


FIGURE 1. Myocardial (coronary sinus) blood flow (CSBF), oxygen uptake (MV_{O_2}) and coronary vascular resistance (CVR) before and after verapamil (V) infusion at rest and during atrial pacing. (**Brackets** in this figure and in Figures 2 to 4 indicate ±1 standard deviation of the mean.)

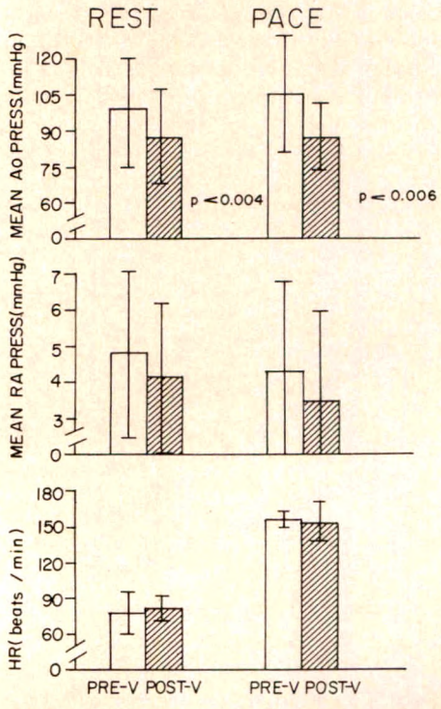


FIGURE 2. Mean aortic (Ao) pressure, right atrial (RA) pressure and heart rate (HR) during four phases of the study (see Fig. 1).

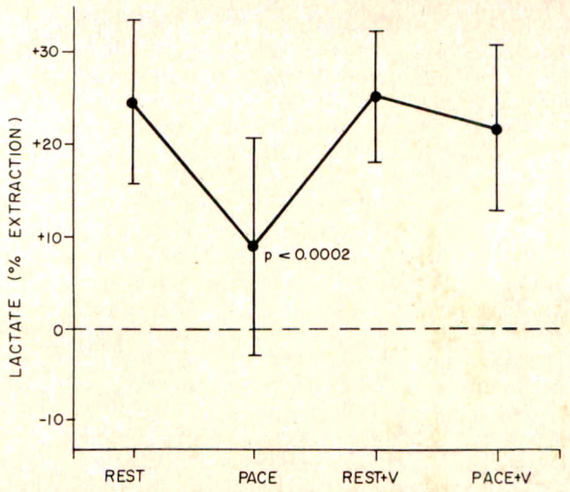


FIGURE 3. Myocardial balance of lactate (as measured with lactate extraction) before and after verapamil (V) infusion at rest and during stress with atrial pacing. Only the second (PACE) phase of the study produced a significant shift from the control (REST) lactate levels.

atrial pacing before and after administration of verapamil. During verapamil infusion, coronary sinus blood flow and myocardial oxygen consumption at rest decreased significantly from control levels: coronary flow from 88 ± 17 to 77 ± 14 ml/min ($p < 0.03$) and oxygen consumption from 10.7 ± 2.4 to 8.8 ± 2.5 ml O_2/min ($p < 0.01$). Verapamil greatly reduced mean aortic pressure (from 98 ± 22 to 88 ± 20 mm Hg, $p < 0.004$) but had no significant effect on coronary vascular resistance, mean right atrial pressure or heart rate.

The combined effects of atrial pacing plus verapamil infusion also differed greatly from those created by atrial pacing alone. Administration of verapamil again produced a significant reduction in coronary flow (from 151 ± 50 to 107 ± 31 ml/min, $p < 0.0002$) and in myocardial oxygen consumption (from 18.5 ± 6.4 to 13.3 ± 4.4 ml O_2/min, $p < 0.001$). The mean aortic pressure decreased from 105 ± 25 to 87 ± 14 mm Hg ($p < 0.006$) and coronary vascular resistance increased from 0.75 ± 0.27 to 0.87 ± 0.25 mm Hg/ml per min ($p < 0.02$). The pacing heart rates were virtually identical (156 ± 5 and 152 ± 15 beats/min) before and after verapamil, and the mean right atrial pressure again did not change appreciably.

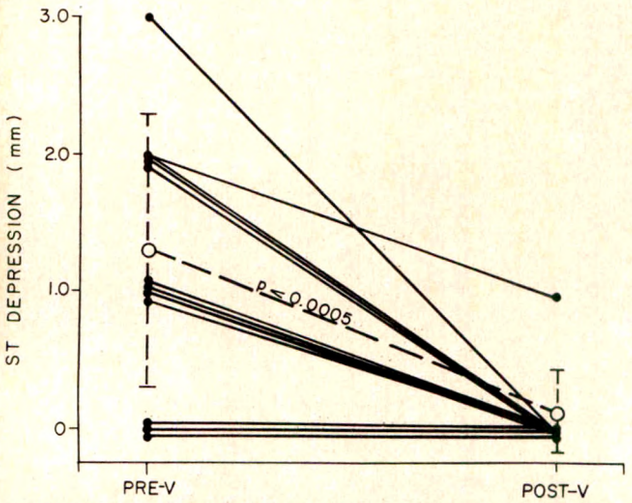


FIGURE 4. Magnitude of S-T segment depression induced by atrial pacing before (PRE) and after (POST) administration of verapamil (V). The **dashed line** represents the mean value for the entire group.

Lactate metabolism: Before administration of verapamil, atrial pacing markedly decreased the heart's ability to extract lactates in all patients, and in three patients (25 percent) there was a shift to lactate production. Mean lactate extraction for the entire group decreased from 24 ± 9 to 10 ± 11 percent ($p < 0.0002$, Fig. 3). The infusion of verapamil completely abolished this metabolic abnormality and returned pacing lactate values to control levels. The mean aortic-coronary sinus lactate gradient between the resting and pacing values before verapamil was 2.76 mg/100 ml; it then decreased to 0.58 mg/100 ml during the verapamil infusion.

S-T segment changes: Nine (75 percent) of the 12 patients registered electrocardiographic S-T segment depression (1 mm or greater) at the end of atrial pacing before verapamil infusion (Fig. 4). The mean S-T segment depression for the entire group was 1.3 ± 1.0 mm. Verapamil abolished S-T segment abnormalities (recorded immediately after termination of atrial pacing) in all but one patient, and the mean S-T depression decreased to 0.1 ± 0.3 mm ($p < 0.0005$).

Threshold to pain: The most dramatic effect of verapamil was the protection that it offered to patients with coronary artery disease before they experienced their typical chest pain. Angina pectoris occurred in all patients stressed with atrial pacing before treatment with verapamil; the mean threshold to pain was 93 ± 67 seconds (Fig. 5). After infusion of verapamil, the threshold to pain increased to 191 ± 183 seconds in six patients, and the remaining six experienced no pain ($p < 0.0005$). The individual responses to atrial pacing stress before and after administration of verapamil are presented in Figure 6. No patient experienced chest pain earlier after treatment with verapamil than before treatment, and six patients became totally pain-free.

Electrolytes and blood gases: Neither atrial pacing nor verapamil—alone or in combination—had a significant effect on the arterial-coronary venous gradients of any of the measured electrolytes or blood gases. Specifically, the aortic to coronary sinus ratio of calcium was unaffected by verapamil at rest or during atrial pacing conducted simultaneously with verapamil infusion.

Side effects: In all instances, angina could predictably be terminated within a few normal sinus beats after cessation of pacing. No patient required sublingual nitroglycerin and no residual enzyme or electrocardiographic changes occurred after the study.

Discussion

Since its discovery more than a decade ago, verapamil has always been considered a powerful negative ino-

tropic agent.[33–37] However, recent studies in our laboratory[21] have demonstrated that when verapamil is given in *therapeutic* doses, the drug's potent peripheral vasodilatory action is sufficiently strong to overcome its intrinsic negative inotropic effect, and thus the drug increases left ventricular ejection fraction and velocity of circumferential fiber shortening when given to patients with coronary artery disease. Yet, because most agents capable of improving left ventricular performance[38] concomitantly increase myocardial oxygen consumption and *decrease* threshold to angina,[39] it was essential to determine the metabolic cost of this improved performance with verapamil therapy in patients with coronary artery disease.

We administered a fairly large intravenous dose of verapamil to all patients (18.8 ± 3.6 mg). Because the intrinsic myocardial depressant effect of verapamil is dose-related,[40,41] the drug was given in these relatively large quantities to elicit the greatest effect on left ventricular metabolism and hemodynamic status that could be produced with *therapeutic* doses of verapamil. Verapamil was given as an intravenous infusion (after the bolus dose was administered) to ensure the even action of the drug throughout the experiment: the half-life of verapamil given as a bolus dose intravenously is very short,[42] and its effect is greatly attenuated within 10 minutes after its administration.[41]

Atrial pacing as a stress: Atrial pacing was selected as a stress in these patients because it can reproducibly drive a given heart to a critical level of tension-time index above which angina occurs repeatedly.[43] Furthermore, it has been shown that increased heart rate causes augmentation of left ventricular contractility,[44] which leads to enhanced myocardial oxygen consumption,[45] despite the propensity of verapamil to depress further the force of contraction at higher heart rates.[10,46–49] Finally, although supine leg exercise represents a greater stress than atrial pacing,[50,51] it was not considered an appropriate test for our patients because it obscures metabolic evidence of ischemia by increasing arterial lactate concentrations.[52]

Verapamil and myocardial lactate metabolism: Atrial pacing induced substantial abnormalities in myocardial lactate metabolism before administration of verapamil. Jackson et al.[53] showed that when the change in coronary arteriovenous lactate difference was less than 0.8 mg/100 ml between the control and the peak atrial pacing sample, the coronary arteries generally were normal. However, when the change was greater than 2.0 mg/100 ml coronary artery disease was *always* present. In our study, the mean arteriovenous lactate gradient was 2.76 mg/100 ml before infusion of verapamil, thus confirming the presence of coronary artery disease. However, after treatment with verapamil the lactate gradient decreased to 0.58 mg/100 ml, thereby obliterating the metabolic evidence that coronary artery disease was indeed present. A parallel response was also seen in the electrocardiographic data: Before verapamil S-T segment depression was registered in most patients; after verapamil, the electrocardiogram returned to baseline in all but one patient.

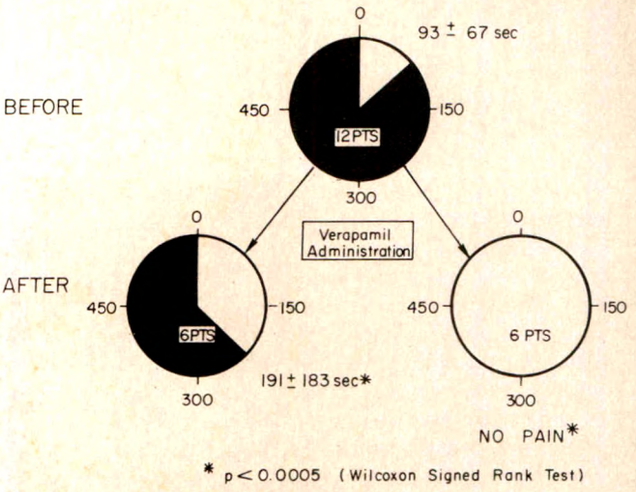


FIGURE 5. Mean threshold to angina (as measured with pacing time) before and after verapamil infusion.

Verapamil and heart rate: Because it has recently been reported[25] that a reflux into the coronary sinus during pacing interventions may invalidate coronary sinus blood flow measurements by the thermodilution method, right atrial pressures were continuously monitored throughout the experiment. No significant change in right atrial pressures was detected during any phase of the study. Moreover, the respective resting and pacing heart rates were virtually identical before and after verapamil infusion, and therefore did not influence the observed results. Despite a significant decrease in the aortic pressure after administration of verapamil, reflex tachycardia was not seen during the resting phase of the study. This is probably due to the fact that

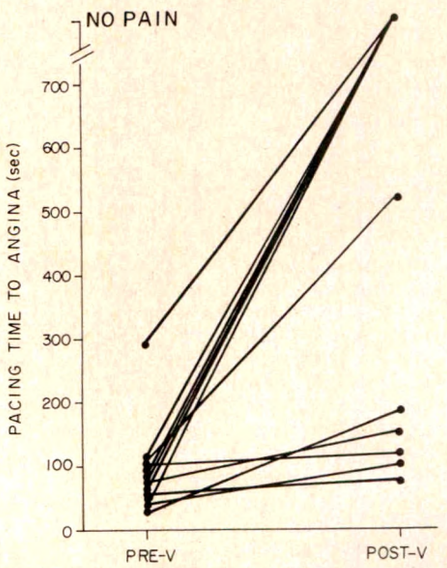


FIGURE 6. Individual threshold to angina (as measured with pacing time) before (PRE) and after (POST) verapamil (V) infusion.

verapamil is not just a vasodilator: It also depresses A-V conduction[54,55] and probably influences sinoatrial conduction[56–58] so that in an isolated heart (where reflex tachycardia can not interfere) it produces bradycardia.[59] The net effect of verapamil on the heart rate in an intact organism is therefore determined by the balance that a given dose of this drug exerts on the two mechanisms that, respectively, speed or slow the heart rate.

Coronary effects of verapamil: The antianginal properties of verapamil have at times been attributed to its coronary vasodilatory action.[60,61] Yet, selective coronary vasodilators have been quite ineffective in abolishing angina pectoris.[62] Most of the studies suggesting that verapamil's antianginal properties may be due to coronary vasodilation have been done in an experimental setting with isolated animal hearts[63,64] or strips from large extramural coronary arteries.[61,65] However, when verapamil was given to human subjects with atherosclerotic coronary artery disease, increased coronary blood flow or coronary dilatation was not observed.[66,67] Indeed, it would be surprising if the rigid cholesterol-laden coronary vessels *could* respond to administration of verapamil by substantial vasodilatation.

In our study, coronary blood flow invariably *decreased* after administration of verapamil—not only at rest but also during the pacing stress that was of sufficient magnitude to always cause angina pectoris in the period before administration of verapamil. Concomitantly, verapamil infusion produced a decrease in the myocardial oxygen consumption that ran parallel to the decrease in coronary flow. These findings are not surprising in view of the marked reduction of mean aortic pressure that always followed administration of verapamil. Because arterial pressure is an important determinant of coronary blood flow and myocardial oxygen consumption,[68] a decrease in aortic pressure will be accompanied by a decrease in coronary flow and myocardial oxygen consumption. During infusion of verapamil the mean aortic pressure at rest decreased by 10 percent, and was accompanied by a 12 percent decrease in coronary blood flow and an 18 percent reduction in myocardial oxygen consumption. The mean aortic pressure during atrial pacing decreased even further after verapamil (by 27 percent), with a concurrent 29 percent reduction in coronary flow and a 28 percent decline in myocardial oxygen consumption. However, coronary vascular resistance did not change appreciably because the decrease in mean aortic pressure was quite closely matched by a similar proportional reduction in coronary flow.

Mechanisms of antianginal effects of verapamil: It is therefore apparent that verapamil is a very effective antianginal agent when given as an intravenous preparation, but that these antianginal properties are probably not primarily due to the drug's coronary vasodilatory action. Rather, verapamil increases threshold to angina by decreasing myocardial oxygen demand, which in turn is decreased by verapamil's potent vasodilatory effect on the peripheral arterial circulation. This enhanced myocardial efficiency is accompanied not only by the subjective perception that angina is ameliorated or abolished by verapamil but also by the objective evidence that myocardial ischemia indeed lessens when verapamil is given (as lactate metabolism again becomes normal and the S-T segment reverts to baseline levels). Whereas decreased oxygen consumption alone may account for all of the findings in this study, it is possible that in some patients with coronary artery disease the antianginal properties of verapamil may be augmented by (1) the drug's intrinsic negative inotropic effect,[33–37] (2) its propensity to decrease preferentially the force of contraction at higher heart rates,[10,46–49] (3) its ability to induce the formation of new coronary collateral vessels,[69] (4) its coronary vasodilatory action,[60,61,63–65] or (5) the production of bradycardia in an occasional subject.[70] Whatever the relative contributions of these additional mechanisms may be, verapamil—at least with the intravenous doses used in this study—is a potent antianginal drug that should become an important new agent for the treatment of patients with ischemic heart disease.

Acknowledgment

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Efficacy of Diltiazem for Control of Symptoms of Coronary Arterial Spasm

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To evaluate the efficacy of the calcium antagonist diltiazem for therapy of active coronary arterial spasm, 13 patients with clinical variant angina attributed to documented coronary arterial spasm completed a prospective randomized double-blind crossover trial of diltiazem (120 and 240 mg/day) versus placebo. Response was assessed with the diary technique measuring frequency of angina, consumption of nitroglycerin and percent of pain-free days.

When 120 mg of diltiazem/day was compared with the paired placebo period there was a significant increase in percent of pain-free days (from 43 to 71 percent [$p = 0.03$]), but no significant decrease in frequency of angina ($p = 0.06$) or consumption of nitroglycerin ($p = 0.32$). When 240 mg of diltiazem/day was compared with the paired placebo period there was a significant increase in percent of pain-free days (from 50 to 79 percent [$p = 0.03$]) and a significant decrease in both frequency of angina (from 1.6 to 0.4 episodes/day [$p = 0.03$]) and consumption of nitroglycerin (from 1.3 to 0.4/day [$p = 0.01$]). Diltiazem was found to be a highly effective drug for control of symptoms of active coronary arterial spasm, without side effects and with excellent patient tolerance.

Variant angina is a manifestation of coronary arterial spasm with or without obstructive coronary artery disease.[1,2] Long-acting nitrates have been the traditional prophylactic therapy for attacks of variant angina. Calcium antagonists are a new class of drugs that interfere with contraction of coronary arterial vascular smooth muscle.[3] Limited trials with four calcium antagonists (diltiazem, nifedipine, perhexilene and verapamil) in the therapy of variant angina have been very encouraging.[4–27] However, fluctuations in disease activity demand randomized trials. In this report we describe the results of a prospective double-blind outpatient study, using the new calcium antagonist diltiazem for the control of symptoms of coronary arterial spasm.

Methods

Study patients: Sixteen patients of either sex participated in the study between February and December 1979. All patients had symptoms of nonexertional angina responsive to sublingual nitroglycerin. Patients were referred to this institution for evaluation and therapy of either suspected or confirmed coronary arterial spasm. Coronary arterial spasm was considered to be documented either electrocardiographically or angiographically. Electrocardiographic confirmation required spontaneous or ergonovine maleate-induced S-T segment elevation of 0.1 mV or more above baseline in association with typical angina. Angiographic confirmation required spontaneous or ergonovine maleate-induced focal coronary arterial spasm reducing the vessel diameter by 50 percent or more compared with that in its resting state.[28] All patients had coronary arteriography performed a mean of 9.6 ± 11.2 months (± standard deviation) before entry into the study. Informed consent was obtained from all participants in the study.

Experimental design: Before entry into the study, administration of cardiac-related medications including long-acting nitrates, alpha and beta adrenergic blocking agents and other calcium antagonists was tapered and discon-

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tinued. Sublingual nitroglycerin for relief of acute angina was the only cardiac medication allowed during the study. Patients entered an initial 14 day single-blind placebo period. Only those patients having five or more episodes of typical angina during this 14 day period entered the subsequent double-blind protocol consisting of four 14 day periods. During the first of these periods, therapy consisted of either 1 placebo or one 30 mg diltiazem tablet every 6 hours with crossover to other therapy for the second period. Therapy during the third period consisted of either two placebo or two 30 mg dilitiazem tablets every 6 hours with crossover to the other therapy for the fourth period. Tablets of dilitiazem or identical placebo were provided in bottles containing 150 tablets. The sequence of assigned bottles was random and unknown.

Patients were evaluated in an outpatient clinic on entry into the study, at each time a bottle was changed and on completion of the study. At every clinical evaluation the following were completed: measurement of weight, assessment of vital signs, physical examination, review of patient diary and pill bottle, interview to assess any adverse reactions, electrocardiogram and determination of plasma level of diltiazem obtained approximately 1 hour subsequent to the last dose of the completed 14 day period. On entry into the study and on completion of the routine serum chemistry determinations, blood and platelet counts and urinalysis were obtained. Patient compliance was assessed from pill counts and plasma levels of diltiazem.

Grouped patient response was assessed from the diary of anginal events and consumption of nitroglycerin and calculated percent of pain-free days. Response for individual patients was assessed by analysis of reduction of pain frequency during active drug periods in comparison with the paired placebo periods. Complete response was arbitrarily defined as a reduction of 90 percent or greater, partial response as 50 to 89 percent reduction and no response as less than 50 percent reduction. Disease attenuation was determined with analysis of reduction of frequency of pain during double-blind placebo periods in comparison with the single-blind placebo period on entry into the study. Disease attenuation was defined as a reduction in average pain frequency to fewer than 0.25 episodes/day and to less than 50 percent of the frequency of pain recorded on entry into the study.

The study was designed to prevent any possible risks of prolonged periods of severe symptoms while on placebo medication. Early blinded crossover to the subsequent double-blind period was allowed if pain was of such frequency and severity as to be unacceptable to both the investigators and the patient.

Blood samples of plasma levels of diltiazem were obtained with standard venipuncture technique with use of a heparinized glass tube that was immediately centrifuged. The supernatant plasma was then immediately frozen and stored. All samples were subsequently analyzed by gas chromatography[29] at Bio-Research Laboratory, Senneville, Quebec, Canada or Marion Laboratories, Kansas City, Missouri.

Statistics: When paired data for assessing drug effects were compared, the two-tailed Fisher's paired randomization test was applied. When paired data of laboratory values were compared, the two-tailed Student's *t* test for paired data was applied.

Results

Clinical Features

Sixteen patients entered the initial 14 day single-blind placebo period. Two patients did not qualify for the double-blind period; one had fewer than five episodes of pain and one refused to cooperate with the study design. One patient who completed the double-blind protocol was withdrawn from study analysis because of the patient's irregularities in handling study medication.* A profile of the 13 remaining patients is presented in Table I. Eight patients were women and five were men. Their ages ranged from 46 to 71 years (average 54 ± 7 [± standard deviation]). Historical duration of symptoms before entry into the study ranged from 0.5 to 107 months (average 79 ± 32). Twelve patients described angina at rest, 11 described nocturnal angina and 8 described exertional angina. All patients smoked cigarettes, five had systemic hypertension requiring pharmacologic therapy and 11 consumed more than 4 ounces of alcohol/week. Prior therapy for variant angina was long-acting nitrates in all patients, alpha adrenergic blocking agents in four, beta adrenergic blocking agents in six and calcium antagonists in two. All patients but one (Case 5) were deemed refractory to prior medical therapy.

Documentation of coronary arterial spasm: Two patients (Cases 5 and 13) had obstructive coronary artery disease with 50 percent or greater reduction of a major vessel diameter. Two patients (one with obstructive coronary artery disease [Case 13] and one with normal coronary arteries [Case 12]) had prior myocardial infarction. Of nine patients having coronary arterial spasm at the time of arteriography, one (Case 11) had spontaneous spasm and eight had spasm provoked by intravenous administration of ergonovine maleate. Of eight patients having S-T segment elevation of 0.1 mV or more above baseline in association with typical angina, five had spontaneous electrocardiographic change and three had electrocardiographic change provoked by intravenous administration of ergonovine maleate. Evidence of ventricular arrhythmia or atrioventricular conduction disturbance was not systematically sought. Three patients demonstrated ventricular tachycardia with angina and one of these three patients additionally demonstrated complete heart block with angina.

To prevent any possible risks of prolonged periods of severe symptoms while on possible placebo medication 14 single- or double-blind periods were shortened in five patients for early crossover (Table II).

Findings

Details of each patient's single-blind placebo period and double-blind crossover periods are reported in Table II.

Group responses: When the single-blind placebo period was compared with each of the double-blind placebo periods, or when the double-blind placebo periods were compared with each other, the percent of pain-free days, frequency of pain and consumption of nitroglycerin were statistically equal. When 120 mg of

* A major airline strike prohibited this patient from attending the clinic and necessitated mail transfer of pill bottles. The patient switched pill bottles as instructed but without permission switched back to the earlier bottle after several days to alleviate angina. If these two uninterpretable bottles are excluded from analysis (first crossover pair), the patient was a complete responder at the higher dosage (240 mg/day).

TABLE I

Clinical Characteristics of 13 Patients

Case	Characteristics of Angina: Age (yr) & Sex	Duration (mo)	Sleep	Exertion	Nonnitrate Before Anginal Treatment	Coronary Arteriograms	Method of Diagnosis
1	50F	45	Yes	Yes	β blocking agent	Irreg RCA	(E) ECG 0.3 mV S-T↑ II III aVF
2	46F	57	Yes	No	α blocking agent	Irreg LAD	Monitor 1.2 mV S-T↑, VT
3	57M	107	Yes	Yes	β blocking agent	Normal	(E) Marked RCA spasm
4	60M	12	No	Yes	None	Irreg RCA, LAD, LCx	(E) Marked LAD, Diag, LCx, OM spasm; ECG 0.2 mV S-T↑ V1–3
5	53F	22	Yes	No	α and β blocking agents, verapamil	50% LAD	(E) Marked RCA spasm; Monitor 0.7 mV S-T↑, VT
6	48F	64	Yes	Yes	β blocking agent	Irreg LAD, LCx	(E) 80% LAD spasm
7	54F	11	Yes	Yes	α blocking agent	Irreg Diag	Monitor 0.5 mV S-T↑, VT, CHB
8	71M	39	No	No	None	Irreg RCA, LAD, LCx	(E) Marked RCA, LAD spasm
9	54F	1	Yes	No	None	Irreg RCA, LAD, LCx	(E) 50% LAD, 95% RCA spasm
10	55F	11	Yes	No	None	Irreg RCA, LAD, Diag	Monitor 0.7 mV S-T↑
11	51M	31	Yes	Yes	β blocking agent, perhexilene	Normal	Spontaneous 70% LAD spasm; (E) Monitor 2.5 mV S-T↑
12	51F	18	Yes	Yes	None	Normal (MI 6/1978, 3/1979)	(E) 70% RCA, 60% LAD spasm; (E) 1 mV S-T↑ II III aVF
13	48M	84	Yes	Yes	α and β blocking agents	70% LAD, 100% LCx & OM (MI 1976)	(E) Marked LAD spasm

α = alpha; β= beta; CHB = complete heart block; LCx = circumflex coronary artery; Diag = diagonal coronary artery; (E) = ergonovine maleate provocation; Irreg = minor irregularity of less than 50 percent diameter reduction; LAD = left anterior descending coronary artery; Marked = greater than or equal to 90 percent reduction in vessel diameter compared with its resting state; LCx = left circumflex coronary artery; MI = myocardial infarction; OM = obtuse marginal coronary artery; RCA = right coronary artery; S-T↑ = S-T segment elevation; VT = ventricular tachycardia.

diltiazem/day was compared with the paired placebo period, there was a significant increase in the number of pain-free days (from 43 ± 30 to 71 ± 37 percent [± SD], p = 0.03) and a trend toward a significant decrease in the frequency of angina (from 2.2 ± 2.7/day to 0.6 ± 1.0/day, p = 0.06), but no significant decrease in the consumption of nitroglycerin (p = 0.32). When the period of administration of 240 mg of diltiazem was compared with the paired placebo period there was a significant increase in the number of pain-free days (from 50 ± 37 to 79 ± 30 percent, p = 0.03) and a significant decrease in both frequency of angina (from 1.6 ± 2.0/day to 0.4 ± 0.5/day, p = 0.03) and consumption of nitroglycerin (from 1.3 ± 1.1/day to 0.4 ± 0.6/day, p = 0.01).

Individual responses: Responses in individual patients varied. When receiving 120 mg of diltiazem/day six patients demonstrated a complete response, one a partial response, three no response and three disease attenuation. When receiving 240 mg of diltiazem/day

TABLE II

Data of Individual Patients During Periods of Single-Blind Placebo (SB), Double-Blind Low Dosage Placebo (P1), 120 mg of Diltiazem (D1), High Dosage Placebo (P2), 240 mg/day of Diltiazem (D2)

Case	Total Days of Period: SB	P1	D1	P2	D2	Average Frequency/Day: Angina: SB	P1	D1	P2	D2	NTG Consumption: SB	P1	D1	P2	D2	Percent of Pain-Free Days: SB	P1	D1	P2	D2
1	14	14	14	14	14	0.4	1.3	0.1	0.9	0.2	0.6	1.5	0.0	0.9	0.2	64	36	93	36	79
2	14	14	14	14	14	0.9	2.1	0.1	2.6	0.0	0.3	1.1	0.1	2.1	0.0	57	21	93	21	100
3	14	14	14	14	14	1.8	0.1	0.1	0.0	0.0	1.9	0.1	0.1	0.0	0.0	7	93	93	100	100
4	14	14	14	14	14	0.9	1.4	0.4	0.1	0.3	0.4	0.6	0.3	0.0	0.1	57	36	71	86	79
5	11	3	11	5	9	4.2	9.7	0.2	1.6	0.0	2.1	9.3	0.0	1.2	0.0	9	0	82	60	100
6	14	14	14	14	14	2.1	0.9	2.8	1.1	0.6	5.0	2.4	6.1	2.5	1.1	7	21	0	29	43
7	14	14	14	14	14	1.4	1.9	0.0	2.6	0.0	2.1	1.7	0.0	2.4	0.0	29	36	100	0	100
8	7	14	7	14	14	1.9	0.2	1.1	0.6	0.7	7.9	0.9	1.9	2.1	1.1	29	86	43	64	64
9	7	2	14	2	14	1.4	5.5	0.0	7.0	0.0	0.1	1.5	0.0	1.5	0.0	29	50	100	0	100
10	14	14	14	14	14	2.2	0.9	0.0	0.2	0.0	1.7	0.4	0.0	0.2	0.0	14	57	100	79	100
11	7	14	14	14	14	3.9	2.4	2.4	3.1	1.4	4.4	2.4	2.4	3.1	1.3	0	0	0	0	0
12	9	7	14	14	10	3.0	1.4	1.1	0.3	1.2	5.4	2.7	1.8	0.6	1.5	0	43	43	86	70
13	14	14	14	14	14	0.7	0.2	0.0	0.1	0.1	0.8	0.2	0.0	0.2	0.4	50	79	100	86	86
Mean	11.8	11.7	13.2	12.4	13.3	1.9	2.2	0.6	1.6	0.4	2.5	1.9	1.0	1.3	0.4	27	43	71	50	79
±SD	3.1	4.5	2.0	4.0	1.7	1.2	2.7	1.0	2.0	0.5	2.4	2.4	1.8	1.1	0.6	23	30	37	37	30

NTG = nitroglycerin; SD = standard deviation.

four patients demonstrated a complete response, two a partial response, three no response and four disease attenuation.

Rebound phenomenon and delayed response: To evaluate for a rebound phenomenon to abrupt cessation of diltiazem therapy, placebo periods after periods of either dosage of diltiazem were analyzed. There was no significant difference in frequency of pain when any combination of the first 3 days of placebo was compared with the remaining days of the placebo periods. To evaluate for a delay in clinical response to the institution of diltiazem therapy, active drug periods after periods of placebo were analyzed. At neither dosage of diltiazem was there a significant difference in frequency of pain when any combination of the first 3 days of active drug was compared with the remaining days of the drug periods.

Systemic effects: There was no change in weight, systolic* or diastolic† blood pressures, electrocardiographic intervals (P-R, QRS, Q-T), routine serum chemistry values, complete blood and platelet counts and urinalysis during the study. There were no complications during the study, and no adverse reactions during the study were ascertained except in one patient who reported headaches during therapy with both the low dosage of diltiazem drug and with placebo.

Discussion

Diltiazem is a member of the new class of agents termed calcium antagonists.[30] These agents act by blocking the influx of freely exchangeable or "extracellular" calcium through calcium channels presumably located in the cell membrane of vascular smooth muscle.[31,32] Pharmacologically, these agents demonstrate noncompetitive antagonism to vasoactive substances such as catecholamines, acetylcholine and histamine, and competitive antagonism to calcium.[33,34] Studies with in vitro human coronary arteries have demonstrated that a wide variety of endogenous vasoactive substances are potentially involved in mediating coronary spasm.[35] The resulting mechanical response of the coronary artery to calcium antagonists is relaxation of its vascular smooth muscle and thus vasodilation. In vitro pharmacologic studies demonstrate that, although diltiazem can exert a negative inotropic action on cardiac ventricular muscle,[36] its preferential effect at clinically used doses is on the coronary vascular smooth muscle.[37]

Diltiazem and other calcium antagonist drugs such as perhexiline, nifedipine and verapamil have been evaluated for therapy of coronary arterial spasm and have been reported to be remarkably effective. However, except for two short-term in-patient studies of calcium antagonists in patients with coronary artery disease and vasospastic angina at rest,[21,27] no double-blind evaluations of any of the calcium antagonist drugs for coronary arterial spasm have been reported.

Effect of diltiazem on angina due to coronary spasm: In our study, six patients given the lower dosage (120 mg/day) and four patients given the higher dosage (240 mg/day) of diltiazem had a complete resolution of their pain. Of the remaining six patients without disease attenuation, one had a partial response to the lower dosage, two a partial response to the higher dosage and three no response at either dosage. These findings may reflect one of four possibilities in the patients without a complete response: (1) inadequate oral dosage possibly secondary to decreased bioavailability; (2) resistance to therapeutic levels of diltiazem; (3) fluctuations in disease activity rendering the patient selectively responsive at only specific periods in the course of the disease; and (4) inaccuracies in the diary technique in evaluating response.

Plasma levels of diltiazem obtained in these patients without a complete response, similar to those in patients with a complete response, exclude the possibility of decreased bioavailability. Comparative drug trials would evaluate the possibility that subsets of patients with coronary arterial spasm may have selective responsiveness to a given class of drugs (for example, calcium antagonists versus nitrates) or a specific drug within a given class (for example, diltiazem versus nifedipine). Studies of longer duration would evaluate the possibility of fluctuation in drug response over time.

More objective data evaluating outpatient drug efficacy by reduction of clinical and subclinical ischemic episodes might have been achieved with ambulatory monitoring.[38] Although patient diaries allowed analysis of several measures of subjective clinical response to therapy, the frequency of subclinical ischemic episodes could not be ascertained nor could the anginal origin of all reported episodes of chest pain be confirmed.

Spontaneous attenuation of coronary spasm: Five of 13 patients demonstrated spontaneous attenuation of disease activity at one or both dosages despite demonstration of much greater disease activity during the single-blind placebo period on entry into the study. The natural history of the activity of variant angina is generally considered variable,[39–42] and pronounced fluctuation of any single measure of disease activity would not be unexpected. However, these five patients demonstrated an attenuation of a clinical measure of disease activity to an extent that partial or complete response to medication could be mimicked if the study was not of crossover design. These findings reinforce the importance of double-blind studies, with the inclusion of placebo periods in study design, to delineate therapeutic response from spontaneous disease attenuation. The possibility of any contribution of diltiazem administration to subsequent disease attenuation could not be assessed because of the small number of patients involved.

There is always concern about possible areas of bias introduced by either the patient or the investigator when using the diary method of documenting episodes

* Systolic: 120 mg/day, 138 mm Hg; paired placebo, 135 mm Hg ($p = 0.31$); 240 mg/day, 136 mm Hg; paired placebo, 133 mm Hg ($p = 0.29$).

† Diastolic: 120 mg/day, 81 mm Hg; paired placebo, 87 mm Hg ($p = 0.81$); 240 mg/day, 84 mm Hg; paired placebo, 87 mm Hg ($p = 0.71$).

of pain. The lack of adverse effects of diltiazem and the multiple crossover periods render it less likely that the patients knew whether they were taking drug or placebo at any given time. However, the patients were aware that the low dosage diltiazem period always preceded the high dosage period.

Absence of rebound phenomenon or delay in clinical response: The failure to detect a difference in frequency of pain when comparing the initial with the remaining days of the placebo periods subsequent to periods of either dosage of diltiazem, suggests the absence of a rebound phenomenon secondary to an abrupt discontinuation of the drug. Bias tending to obscure such a phenomenon could be provided by those patients whose placebo periods were shortened because of angina of unacceptable frequency and severity. If withdrawal symptoms were occurring, shortening of the placebo period would not allow these patients to demonstrate a reduction in frequency of pain. The failure to detect a difference in frequency of pain when comparing the initial with the remaining days of active drug periods subsequent to placebo periods suggests the absence of a delay in clinical response to the institution of diltiazem therapy.

In summary, diltiazem is a safe and highly effective calcium antagonist for therapy of clinical symptoms of coronary arterial spasm. This drug is free of adverse effects and patient tolerance is excellent. There is no evidence for either a rebound phenomenon secondary to abrupt discontinuation of the drug or a delay in clinical response to the institution of drug therapy.

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Modification of Ventricular Tachycardia by Procainamide in Patients With Coronary Artery Disease

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Fifteen consecutive patients with coronary artery disease had rapid (158 to 272 beats/min) and sustained ventricular tachycardia induced by the extrastimulus technique, and received procainamide infusion. Before the study, all but one patient had severe symptoms with tachycardia, and six had survived apparent sudden death. Procainamide consistently slowed ventricular tachycardia. However, in traditional doses (1 g infusion, plasma concentration greater than 4 μg/ml), it prevented induction of ventricular tachycardia in only 2 of the 15 patients. Induction of ventricular tachycardia was facilitated by procainamide in 10 patients. Larger doses of procainamide (plasma concentration 20.2 μg/ml ± 9.7 [mean ± standard deviation]) prevented induction of ventricular tachycardia in one of eight patients. Rapid ventricular rates (more than 210 beats/min) that were not slowed (by 50 percent or more) after a 1 g infusion of the drug predicted failure of procainamide to prevent ventricular tachycardia. Therefore, procainamide slowed but did not prevent induced ventricular tachycardia in most of these patients with coronary artery disease at risk of sudden death.

We[1] have previously described six patients in whom procainamide failed to prevent or even facilitated the induction of recurrent ventricular tachycardia by the extrastimulus technique. This report extends our observations on modification of ventricular tachycardia with procainamide in 15 patients with ventricular dysfunction due to coronary artery disease. Our experience suggests that procainamide might prevent recurrent arrhythmia in only a small subset of patients whose tachycardias are slower and better tolerated.

Methods

Study patients: Fifteen consecutive patients, aged 42 to 68 years, were evaluated for ventricular tachycardia using the extrastimulus technique before and after procainamide infusion. Patients meeting the following criteria constituted the basis of this report: (1) coronary artery disease and remote myocardial infarction; (2) *sustained* ventricular tachyarrhythmias that did not occur in the setting of reinfarction; and (3) successful induction of sustained ventricular tachycardia by the extrastimulus technique. Four patients were excluded from this report because sustained ventricular tachycardia was not induced by extrastimulation in the basal state, but they had spontaneous sustained ventricular tachycardia while receiving procainamide. An additional two patients did not receive procainamide because it had previously caused drug fever or lupus reaction.

Table I provides clinical data on the patients studied. Twelve patients were referred before comprehensive clinical evaluation of drugs (seven of whom had taken no drug) because of frightening tachycardias that often required resuscitation from syncope or apparent sudden death. Patients were not excluded from the study if tachycardia could not be terminated by ventricular stimulation and external direct current countershock was required. Ten patients required direct current countershock before drugs were given. Thus, patients with poorly tolerated ventricular tachycardia, presumably at a faster rate (see later), were all included, avoiding this bias in patient selection.

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Coronary arteriography and contrast left ventriculography were performed in 14 patients, and two dimensional echocardiographic left ventricular imaging was performed in the remaining patient. Ventricular aneurysm was defined as a segment of the left ventricular silhouette exhibiting akinesia or dyskinesia. The size of the dyskinetic segment (Table I) was described, using a modification of the method of Feild et al.,[2] as percent of the diastolic circumference of the right anterior oblique ventriculogram.

Stimulation and recording techniques: Initial procainamide studies were performed in the electrophysiology laboratory at least five half-lives after discontinuation of any antiarrhythmic drugs, and after the patients had given informed written consent. Subsequent drug studies were sometimes done in the cardiac care unit, using only surface electrocardiography.

The right ventricular apex was stimulated and sustained ventricular tachycardia induced with single or double extrastimuli. Extrastimuli at twice threshold were delivered at 10 ms decrements of coupling after eight drive stimuli. The drive cycle length selected was generally about 100 ms shorter than that resulting in consistent ventricular capture, thus allowing the same cycle length to be used after sinus acceleration by subsequent drug infusion or direct current cardioversion. When double extrastimuli were required for induction of ventricular tachycardia, the first extrastimulus was applied at a coupling interval of the effective refractory period plus 20 ms.

When sustained ventricular tachycardia was initiated, the coupling interval of the last extrastimulus was taken as the outer border of the zone of tachycardia. Termination of the tachycardia was attempted with extrastimulation and by bursts of rapid pacing in symptomatic patients. External countershock was used when the tachycardia or its acceleration by rapid pacing caused loss of consciousness. If external countershock was not required the inner border of the zone of tachycardia was then delineated, using incremental extrastimulation beginning within the effective refractory period. However, if countershock was required a second induction of tachycardia was not considered justified.

Recordings were made at paper speeds of 50 and 100 mm/s with an Electronics for Medicine VR-12 oscilloscope recorder. Intracardiac electrograms (from the proximal poles of the quadripolar right ventricular catheter and generally from a tripolar catheter with His bundle electrogram) were recorded at filter settings of 30 to 500 hertz. Surface leads I, aVF and V_1 were recorded as well.

Procainamide administration: After sinus rhythm had returned, procainamide was infused at a rate of 100 mg/min, with the infusion delayed each minute that systolic blood pressure was less than 90 mm Hg. Induction of tachycardia was again attempted 5 to 10 minutes after completion of the infusion. Most patients were tested after receiving a traditional dose of procainamide, defined as an infusion of 1 g, resulting in a plasma concentration of 4 to 10 μg/ml.[3–5] Blood was drawn for procainamide plasma concentration just after completion of induction and termination of tachycardia. Eight patients received larger infusions or larger oral doses, defined by a plasma concentration greater than 10 μg/ml, if the 1 g infusion was ineffective.

Induced ventricular tachycardia was considered sustained if ventricular stimulation or countershock was required for its termination. Procainamide was considered to have facilitated induction of tachycardia if there was a widened zone of tachycardia or if fewer extrastimuli were required for its induction (a clinical implication of facilitated induction of tachycardia is unproved). The response to procainamide was considered unchanged if the same number of extrastimuli were used and the zone of tachycardia was not altered or measured.

Results

Left ventricular dysfunction: Left ventricular dysfunction was characterized by angiography in 14 patients and by two dimensional echocardiography in another. Almost all patients had appreciable left ventricular dysfunction (ejection fraction 0.33 ± 0.12, mean ± standard deviation [SD]) and 14 of the 15 patients had focal akinesia or dyskinesia consistent with ventricular aneurysm. Ejection fraction did not determine rate of tachycardia ($r = -0.22$). The cycle length of ventricular tachycardia was usually about 300 ms or less (that is, 200 beats/min or faster). We think this explains why 10 of 15 patients with coronary artery disease required external countershock to terminate ventricular tachycardia induced in the basal state. The characteristics of ventricular tachycardia were different from

TABLE I

Clinical Characteristics of Patients Receiving Procainamide

Case	Age (yr) & Sex	Symptoms With VT	Prior Drug failures	Site of Aneurysm	LVEDP (mm Hg)	LVEF	Aneurysm Fraction
1	58M	Presyncope, angina	None used	Inferior	8	0.42	0.14
2	51M	Presyncope	Quin	Inferior	20	0.51	0.06
3	63M	Sudden death	Pa, Lido, Pro, Quin	Anterior	24	0.42	0.43
4	67M	Syncope	Pa, Pro, Quin	Anterior*	14	0.36	...*
5	42M	Palpitations	None used	Anterior	20	0.11	0.46
6	60F	Presyncope	Lido, Quin	Inferior	24	0.30	0.45
7	64M	Syncope	None used	Inferior	37	0.20	0.72
8	68M	CHF, angina	Pa, Quin	Inferior	18	0.39	0.20
9	64M	Sudden death	Pro, Quin	Anterior	30	0.14	0.69
10	61M	Sudden death	None used	Anterior	...	0.33	...
11	55M	Presyncope	Quin	Inferior	25	0.42	0.32
12	56M	Sudden death	None used	Anterior	20	0.29	0.43
13	61M	Sudden death	Diso, Pa	Anterior	30	0.23	0.51
14	54M	Sudden death	None used	Inferior	21	0.39	0.61
15	46M	Presyncope, angina	None used	Inferior	14	0.47	0.41

* Hypokinesia.

Aneurysm fraction = size of aneurysm designated as percent of diastolic circumference of the right anterior oblique ventriculogram; CHF = congestive heart failure; Diso = disopyramide; Lido = lidocaine; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; Pa = procainamide; Pro = propranolol; Quin = quinidine; VT = ventricular tachycardia.

those in previously reported series[6,7] because these 10 patients were not excluded from further study. Thus, ventricular tachycardia was faster in our patients (average 211 ± 30 beats/min) and slower than 185 beats/min only in Patient 5. The cycle length of ventricular tachycardia was also not related to the extent of asynergy estimated from the fraction of the left ventricular silhouette consisting of the aneurysm ($r = -0.47$).

Effects of procainamide: Infusion of procainamide resulted in consistent dose-related slowing of ventricular tachycardia (Table II). Figure 1 illustrates ventricular tachycardia in a representative patient (Case 14) and demonstrates that the cycle length of the tachycardia lengthened progressively with increments in procainamide dose and plasma concentration. The cycle length was lengthened by procainamide in the entire series of patients (Fig. 2).

Sustained ventricular tachycardia could be induced after infusion of traditional doses of procainamide in 13 of 15 patients. The plasma concentrations were 5.7 μg/ml or more. In fact, induction of ventricular tachycardia was facilitated by procainamide in 10 of these patients (Table II).

The two patients in whom traditional doses of procainamide prevented induction of sustained ventricular tachycardia (Patients 1 and 5) had mild symptoms and the slowest rates of tachycardia (188 and 158 beats/min, respectively) in the group. The two thin dashed lines in Figure 2 show that these two patients had the greatest slowing in response to procainamide (a 34 and 50 percent increase, respectively, in tachycardia cycle length after 0.5 g of procainamide). After infusion of 1 g, sustained ventricular tachycardia could not be induced. Neither patient had spontaneous ventricular tachycardia when oral procainamide therapy was administered later. In contrast, the average increase in ventricular tachycardia cycle length after twice as much procainamide (1 g) in nonresponders was only 23 ± 15 percent.

Eight of the 13 patients not responding to traditional doses were further tested after taking larger doses of procainamide (average infusion of 2.1 g or [not shown in Fig. 2] 8 to 12 g orally/day). A ninth patient (Case 2) was not tested because he had spontaneous sustained ventricular tachycardia while receiving 10 g of the drug. The plasma concentrations studied ranged from 11.3 to 42.1 μg/ml (average 20.2 ± 9.7 μg/ml). Only one patient (Patient 9) among these nine did not have sustained ventricular tachycardia. He responded to a procainamide dosage of 8 g orally/day (plasma pro-

TABLE II

Effects of Procainamide (Pa) on Induced Ventricular Tachycardia (VT)

Case	Pa Dose, (g)	Pa Plasma Concentration (μg/ml)	VT Cycle Length (ms-basal)	VT Cycle Length (ms-Pa)	VT Induction After Pa
1	0.5 iv	. . .	320	430	Unchanged
	1.0 iv	. . .	320	. . .	Prevented
2	1.0 iv	. . .	320	380	Facilitated
3	1.2 iv	11.3	290	390	Facilitated
4	1.0 iv	9.4	310	355	Facilitated
5	0.5 iv	5.7	380	570	Unsustained
6	0.5 iv	. . .	280	300	Facilitated
	1.0 iv	. . .	280	320	Facilitated
	1.5 iv	. . .	280	400	Facilitated
	2.0 iv	14.3	280	470	Facilitated
7	1.0 iv	8.9	220	265	Unchanged
8	1.0 iv	9.4	305	380	Facilitated
9	1.0	8.4	290	440	Facilitated
	8/day po	18.0	290	. . .	Prevented
10	0.5 iv	. . .	250	310	Unchanged
	1.0 iv	. . .	250	380	Unchanged
	2.0 iv	22.0	250	420	Unchanged
11	2.0 iv	13.7	240	320	Facilitated
12	1.0 iv	5.2	285	300	Unchanged
13	0.5 iv	2.8	320	300	Unchanged
	1.0 iv	6.7	320	350	Facilitated
	1.5 iv	7.0	320	445	Facilitated
	12/day po	21.5	320	430	Facilitated
14	0.5 iv	. . .	290	370	Unchanged
	1.0 iv	7.9	290	410	Facilitated
	2.0 iv	24.5	290	480	Facilitated
	3.0 iv	42.1	290	580	Facilitated
	6/day po	13.3	290	400	Facilitated
15	1.0 iv	5.4	240	320	Unchanged
	2.0 iv	11.6	240	350	Facilitated
	3.0 iv	18.3	240	380	Facilitated

iv = intravenously; po = orally.

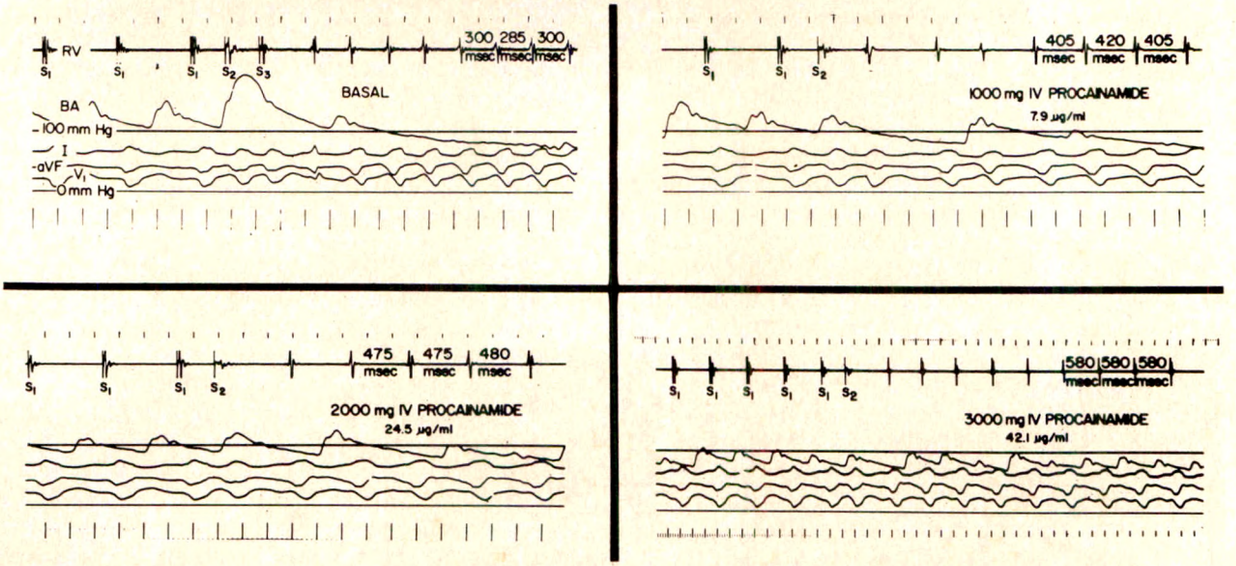


FIGURE 1. Case 14. Effect of progressive doses of intravenous (IV) procainamide on induced ventricular tachycardia in a representative patient. There are 200 and 40 ms time lines and the trace after 3.0 g is recorded at a slower paper speed. The basic stimulation cycle length (S_1-S_1) is constant. The tachycardia cycle length is progressively lengthened with increasing doses and higher plasma procainamide levels. Also, an S_2-S_3 sequence induces tachycardia in the basal state (**upper left**), but after a substantial dose of procainamide (**lower panels**) a single extrastimulus (S_2) is sufficient to initiate ventricular tachycardia. BA = brachial arterial pressure pulse; RV = right ventricular electrogram; S_1 = drive stimuli at 100/min; S_2-S_3 = extrastimuli.

cainamide concentration 18.0 μg/ml, plasma N-acetyl procainamide 18.2 μg/ml), which caused an unstable gait. His response to infusion of 1 g of procainamide is depicted in Figure 2. The 52 percent increase in ventricular tachycardia cycle length after the infusion more closely resembled the response of the 2 patients in whom traditional doses of procainamide prevented ventricular tachycardia (Fig. 2) than the dose-response curve of the remaining 12 patients.

On the basis of the entire set of 24 observations in the 12 nonresponders, the average change in cycle length for each bolus dose of procainamide infused was 79.3 ± 48 ms/g procainamide (Fig. 3). In contrast, the three observations that could be made in responders before ventricular tachycardia was prevented suggested a significantly greater slowing (250 ± 118 ms/g procainamide, $p < 0.001$).

There were no clinical features other than the rate of ventricular tachycardia that predicted a successful response to procainamide. One of the three patients with sustained tachycardia prevented with procainamide had ventricular tachycardia with a right bundle branch block form, one with a left bundle branch block form and one with both forms. Two had an anterior and one an inferior aneurysm, of 8 months' and 4 and 10 years' duration, respectively. The two with an anterior aneurysm had nonobstructed left circumflex and right coronary arteries but the patient with the inferior aneurysm had significant left main coronary arterial stenosis. Left ventricular dysfunction was as severe as in nonresponders (ejection fraction 0.11, 0.14 and 0.42, respectively) and the fractional size of the aneurysm was as great (0.69, 0.46 and 0.14, respectively).

Response to other drugs: Table III summarizes the clinical and laboratory response to a variety of additional antiarrhythmic drugs given alone or in combination. Additional drugs were used in a nonsystematic fashion. No patient responded to quinidine who had not responded to procainamide. However, failure to respond to procanamide did not preclude a response to other type I (disopyramide) or dissimilar antiarrhythmic agents. A response to a different type I agent that slowed

TABLE III

Response to Additional Antiarrhythmic Agents

	Drugs Not Preventing VT		Drugs Preventing Sustained VT	
Case	Type I	Other	Type I	Other
1	. . .	. . .	Pa	. . .
2	Pa, Diso, Quin	Lido, Phen, Pro	. . .	Aceb
3	Pa, Diso, Quin	Lido, Mex, Pro	. . .	. . .
4	Pa, Quin	Pro	Diso	. . .
5	. . .	. . .	Pa, Quin	. . .
6	Pa, Diso, Quin	Lido, Pro	. . .	. . .
7	Pa, Diso	. . .	. . .	Lido, Mex
8	Pa, Quin	. . .	. . .	. . .
9	Diso, Quin	Lido, Phen	Pa	Bret
10	Pa, Diso, Quin	Lido, Phen, Bret	. . .	. . .
11	Pa, Quin	. . .	Diso	. . .
12	Pa, Quin	. . .	. . .	. . .
13	Pa, Diso, Quin	Mex, Toc, Bret (oral)	. . .	Lido, Bret
14	Pa, Diso, Quin, Aprin	Lido, Ver, Bret	. . .	. . .
15	Pa, Diso, Quin	Lido, Bret	. . .	Pro

Aceb = acebutolol, 1.2 g/day orally; Aprin = aprindine, 200 mg intravenously; Bret = bretylium tosylate, 10 mg/kg intravenously (oral dose 1.0 g/day); Diso = disopyramide, 0.8 to 1.2 g/day orally; Lido = lidocaine, 225 mg intravenously; Mex = mexiletine, 1.2 g/day orally; Pa = procainamide (see text for doses and routes of administration); Phen = phenytoin, 400 mg/day orally; Pro = propranolol, 160 to 240 mg/day orally; Quin = quinidine, 1.6 to 2.4 g/day orally; Toc = tocainide, 3.2 g/day orally; Ver = verapamil, 15 mg intravenously.

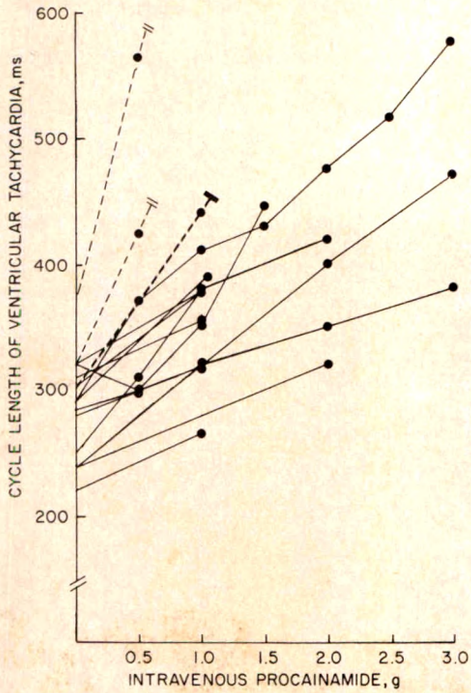


FIGURE 2. Effect of procainamide infusions on ventricular tachycardia cycle length. There is consistent slowing of tachycardia as a function of procainamide dose. The dose-response curves show the greatest slowing of rate in the patients responding to traditional intravenous doses (**top two thin dashed lines**) or in the patient subsequently responding to a high oral dosage (**lower thick dashed line**).

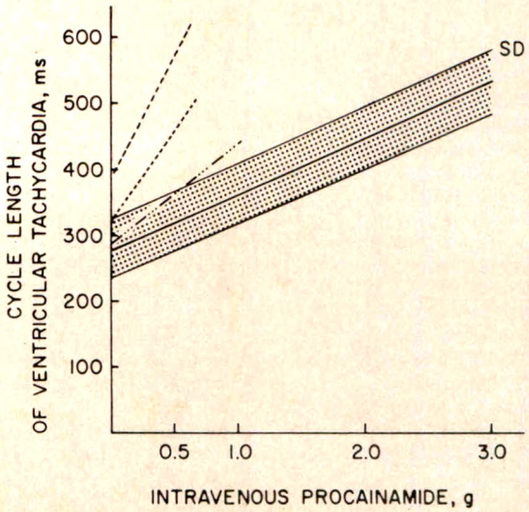


FIGURE 3. Dose-response relation between infused procainamide and ventricular tachycardia cycle length. Responders (**dashed lines**) had a greater slowing of ventricular tachycardia in response to procainamide than did nonresponders (**bar**) ($p < 0.001$).

conduction could have resulted from differences in dosage or potency, but neither of the two responders to disopyramide had initially slow ventricular tachycardia or dramatic slowing of tachycardia with procainamide.

Discussion

Poor response of ventricular tachycardia to procainamide: Our patients had ventricular tachycardia in the setting of coronary artery disease and ventricular aneurysm. Six of our patients had been resuscitated from apparent sudden death and ventricular fibrillation was recorded in four at the time of resuscitation, presumably as a consequence of poorly tolerated ventricular tachycardia. This subset of patients with coronary artery disease who were truly at risk for sudden death received traditional doses of procainamide and achieved plasma concentrations of procainamide that have been used to suppress chronic ventricular arrhythmia, but results were disappointing. Only 2 of the 15 patients had at least partial prevention of ventricular tachycardia by traditional infusion doses of procainamide. Among nine patients receiving larger doses of procainamide, one responded, at a plasma concentration that caused neurologic toxicity. Several patients not entered into the study had spontaneous recurrence of ventricular tachycardia while receiving larger doses of procainamide.

These data are consistent with prior reports and unpublished communications. Only two of the six patients with coronary artery disease tested by Wellens et al.[7] responded to procainamide, and the rate of ventricular tachycardia was 167 and 171 beats/min, respectively, in these two patients. Among 28 patients with coronary disease, Fisher et al.[8] had only 3 responders (rates 160, 160 and more than 210 beats/min, respectively) (Fisher JD, personal communication). Horowitz et al.[6] had only 6 responders among 14 patients with heart disease (rates only 130 to 171 beats/min). (Horowitz LN, Josephson ME, personal communication). Mason and Winkle[9] found only 3 of 11 to respond (rates 135, 158 and 279 beats/min) (the last as a result of isoproterenol infusion; Mason JW, personal communication). These data compare with those of the three responders (20 percent) in our series whose rate of ventricular tachycardia was 158,188 and 207 beats/min, respectively. In summary, only a minority of patients with heart disease previously reported on responded to procainamide. Responders generally had a slower rate of tachycardia than the average of 215 beats/min in our series.

Clinical implications: Our data suggest that the dose-response potency of procainamide in further slowing of ventricular tachycardia predicts ultimate prevention of the arrhythmia. Other characteristics of the ventricular tachycardia, such as the form or site of origin, the size of the aneurysm or the functional state of residual myocardium, do not appear to be critical. Although procainamide was the most effective drug we used, it facilitated induction of tachycardia in the majority of patients. It is hypothesized that the mechanism of successful procainamide action is to slow conduction in a reentrant circuit,[1,10] rather than to prolong refractoriness to a greater extent than the slowing.

Acknowledgment

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Positive Inotropic Effects of Hydralazine in Human Subjects: Comparison With Prazosin in The Setting of Congestive Heart Failure

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Hydralazine possesses positive inotropic properties in animal model preparations. To determine whether this vasodilator elicits a positive inotropic response in the failing human ventricle, hydralazine, 75 or 100 mg, was administered orally to 14 patients with left ventricular dysfunction and congestive heart failure; the results were compared with those of first-dose prazosin at 5 and 10 mg. The duration of the preejection period and the isovolumic developed pressure/duration of isovolumic contraction ($\Delta P/\Delta t$) were used as indexes of inotropy. Prazosin did not effect a significant response in the duration of the preejection period or in the $\Delta P/\Delta t$. Hydralazine significantly shortened the preejection period and increased the $\Delta P/\Delta t$ over 8 hours after administration; these data suggest that hydralazine elicits a positive inotropic response in the failing human ventricle.

Hydralazine is a vasodilator widely used in the management of chronic congestive heart failure. As an arteriolar vasodilator, its primary beneficial effects are secondary to afterload reduction. Studies in animal models[1–3] indicate that hydralazine possesses direct positive inotropic properties on the myocardium. This study was designed to determine whether hydralazine elicits positive inotropy in human subjects in the setting of ventricular dysfunction and congestive heart failure; the results were compared with those of another widely used vasodilator, prazosin.

Methods

Study patients: Fourteen adult patients with severe congestive heart failure were studied. All patients underwent diagnostic cardiac catheterization within 1 month of the study. Each patient had a form of congestive cardiomyopathy whose origin was ischemic in nine and idiopathic in five. Seven patients were studied after receiving 75 mg of hydralazine orally and seven after receiving 100 mg orally. After a 24 hour reequilibration period, the former group also received 5 mg of prazosin orally and the latter group 10 mg of prazosin orally. Diuretic drugs, nitrates and other vasodilators were discontinued a minimum of 72 hours before the study. No patient was taking maintenance hydralazine or prazosin before hospitalization. Patients with atrial fibrillation or flutter, an artificial pacemaker or valve insufficiency were excluded. Written informed consent was obtained from each patient before the study.

Procedures and measurements: A triple lumen flow-directed catheter was placed in the pulmonary artery of each patient 1 day before the study. This catheter provided the measurement of the pulmonary capillary wedge pressure (pulmonary arterial occlusive pressure) and cardiac output; pressures were determined with Electronics for Medicine M2101 pressure amplification units and cardiac output with thermodilution using an Instrumentation Laboratory 601 computer and 602 recorder. Systemic blood pressure was measured indirectly with a calibrated sphygmomanometer. Simultaneous recordings of a carotid pulse tracing, a precordial phonocardiogram and an electrocardiogram were made using an Electronics for Medicine Echo IV unit.

Technical specifications[4] *included* carotid pulse recordings at an amplitude greater than 5 cm with a Statham P23Db transducer (frequency response 0.1

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TABLE I

Control Values for the Different Measurements (mean ± standard error of the mean)

	Hydralazine		Prazosin	
	75 mg (n = 7)	100 mg (n = 7)	5 mg (n = 7)	10 mg (n = 7)
PEPI (ms)	173 ± 18	185 ± 20	184 ± 23	180 ± 20
ΔP/Δt (mm Hg/s)	562 ± 90	549 ± 97	549 ± 89	553 ± 93
ΔP (mm Hg)	50 ± 6	45 ± 7	45 ± 6	47 ± 5
Δt (s)	0.089 ± 0.015	0.082 ± 0.017	0.082 ± 0.020	0.085 ± 0.017
SVI (ml/m²)	24 ± 3	22 ± 3	24 ± 2	23 ± 2
HR (beats/min)	84 ± 5	86 ± 6	87 ± 6	88 ± 4
PCWP (mm Hg)	28 ± 4	26 ± 2	26 ± 3	25 ± 3

HR = heart rate; n = number; PCWP = pulmonary capillary wedge pressure; PEPI = preejection period index.

to 30 hertz) connected to a funnel-shaped pickup (diameter = 2.3 cm) by a 3 cm (diameter = 4 mm) polyethylene tube; recordings of the second heart sound showing clear inscription and identification of the aortic component (cutoff frequency setting greater than 100 hertz); and an electrocardiographic lead showing the clearest definition of the Q wave. The same recording unit was used to obtain an apexcardiogram. All recordings were made at a paper speed of 100 mm/s. Ten successive complexes were averaged for each determination.

Measurements were made every 20 minutes during the 1 hour control period for each drug; patients with a coefficient of variance greater than 10 percent (for cardiac output and pulmonary capillary wedge pressure) during the control period were excluded. The last set of measurements during the control period was used as the control values. After the administration of each drug, measurements were made every hour over an 8 hour period.

Calculations included: stroke volume index = cardiac output/heart rate/body surface area; preejection period (PEP) = total electromechanical systole ($Q\text{-}S_2$) − left ventricular ejection time; preejection period index (PEPI) = PEP corrected for heart rate[4]; and $\Delta P/\Delta t$,[5,6] where ΔP = developed pressure during isovolumic contraction = systemic diastolic blood pressure − pulmonary capillary wedge pressure, and Δt = isovolumic contraction time = PEP − electromechanical delay (Q wave of the electrocardiogram to upstroke of left ventricular impulse on the apexcardiogram). A decrease in the preejection period index and an increase in the $\Delta P/\Delta t$ indicate positive inotropy.[4–7]

Statistical analysis: Each response curve for each drug and dose was compared with responses in the control period using the analysis of variance for repeated measures; additional analysis of each hourly mean value was made using the Student's *t* test for paired data. Comparison of response curves between the two drugs was accomplished by two way analysis of variance. A probability (p) value of <0.05 defined a significant difference.

Results

Control measurements: There were no significant differences among any of the control measurements in the four drug studies (Table I). The presence of congestive heart failure in this patient group is reflected in the elevated pulmonary capillary wedge pressure and reduced stroke volume.

Preejection period index: Hydralazine at both doses significantly shortened the preejection period index (Fig. 1); the degree of shortening appeared to be dose-related. Although prazosin demonstrated a tendency to decrease the preejection period index, the changes were not significantly different from values in the control period for both the 5 and 10 mg doses.

ΔP/Δt: Hydralazine significantly increased the $\Delta P/\Delta t$ at both the 75 and 100 mg doses (Fig. 2A); once again, the response appeared to be dose-related. Prazosin did not change the mean $\Delta P/\Delta t$ from those values in the control period. Figure 2, B and C, presents the components of the $\Delta P/\Delta t$ measurement for each drug and dose. The developed pressure (ΔP) during isovolumic contraction did not change significantly from that in the control period for either drug. The duration of

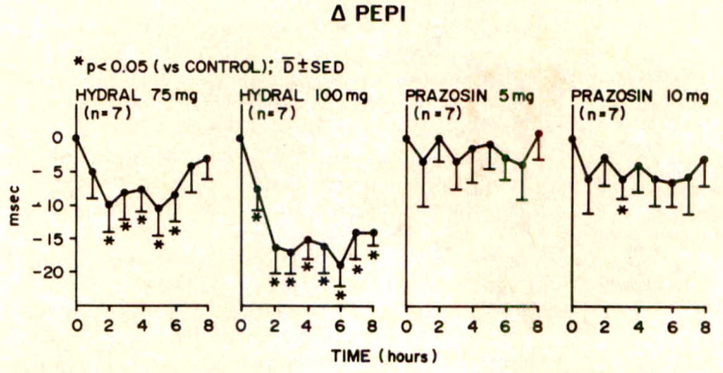


FIGURE 1. Graphs illustrating the changes in the preejection period, corrected for heart rate (PEPI), elicited by oral hydralazine (HYDRAL), 75 and 100 mg, and prazosin, 5 and 10 mg. Hydralazine significantly shortened the PEPI in a dose-related response. Prazosin did not significantly alter this parameter. The response curves for both doses of hydralazine were significantly different from those for prazosin. $\bar{D} \pm SED$ = mean change (difference) from control values ± standard error of the difference.

isovolumic contraction (Δt) shortened significantly with hydralazine and remained unchanged for prazosin. This difference in the isovolumic contraction time accounted for the divergence of the $\Delta P/\Delta t$ curves for hydralazine and prazosin.

Other hemodynamic measurements: The changes in stroke volume index, indicative of the degree or extent of contraction, for the two drugs are presented in Figure 3A. Both drugs increased the mean stroke volume index, and the response was dose-related for both agents. The mean heart rate did not change from that in the control period for either drug (Fig. 3B). The changes in mean pulmonary capillary wedge pressure (Fig. 3C) were similar for 75 mg of hydralazine and 5 and 10 mg of prazosin. Hydralazine at 100 mg effected an additional mild decrease in the mean pulmonary capillary wedge pressure.

Discussion

This study suggests that hydralazine elicits positive inotropy in the failing left ventricle in human subjects; this drug significantly shortened the preejection period and increased the mean rate of rise of isovolumic pressure or $\Delta P/\Delta t$. The effects of prazosin on these inotropic variables were negligible. These results in human subjects parallel those obtained by Riggs et al.[3] in isolated cat papillary muscle; in their preparation, hydralazine increased peak tension, rate of tension development and maximal rate of shortening ($\dot{V}$ max) whereas prazosin did not alter these variables.

Shorter preejection period and isovolumic contraction time as indexes of positive inotropy: The enhanced inotropy with hydralazine was primarily a result of shortening of the preejection period and isovolumic contraction time. Changes in the preejection period and isovolumic contraction time alone correlate well with other indexes of inotropy and contractility.[4,7,8] Mean isovolumic developed pressure (ΔP) was not altered by hydralazine because the decrease in left ventricular filling pressure was accompanied by a parallel decrease in diastolic blood pressure. A decrease in left ventricular filling pressure alone would lengthen the preejection period index and the duration of the isovolumic contraction (resultant decrease in $\Delta P/\Delta t$) without invoking a negative inotropic mechanism. A decrease in aortic diastolic pressure alone would shorten the preejection period index and the duration of isovolumic contraction (increase in $\Delta P/\Delta t$) without posi-

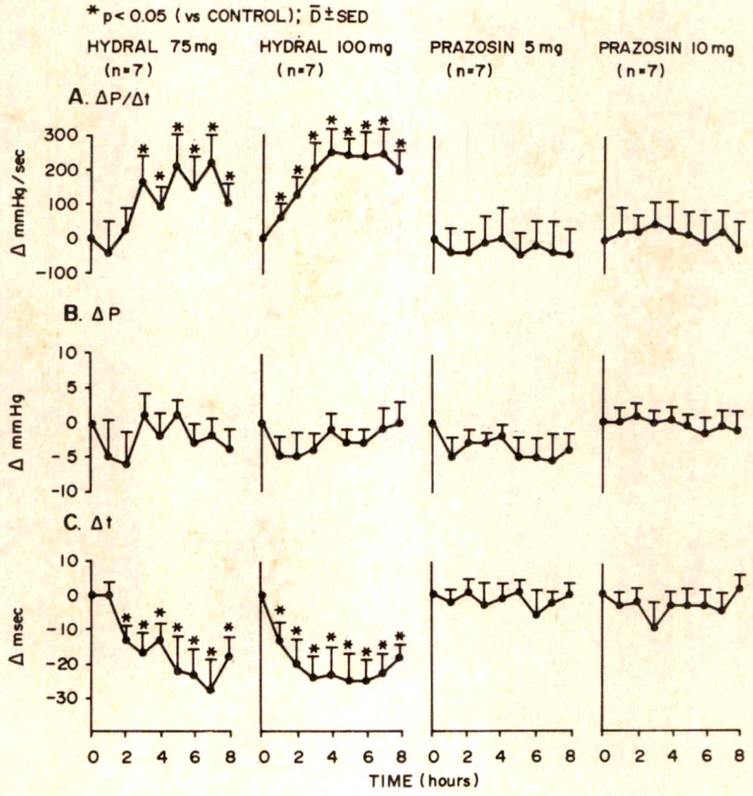


FIGURE 2. A, hydralazine (HYDRAL), 75 and 100 mg, significantly increased the inotropic index $\Delta P/\Delta t$. Prazosin generally did not change this determinant of inotropy. The response curves for both doses of hydralazine were significantly different from those for prazosin. The changes of the components of $\Delta P/\Delta t$ are presented in **B** and **C. B,** developed pressure during the isovolumic contraction (ΔP) did not change from the control value for either hydralazine or prazosin. **C,** the duration of isovolumic contraction (Δt, in milliseconds) decreased significantly with hydralazine and remained unchanged for prazosin. The response curves of both doses of hydralazine were significantly different from those of prazosin.

tive inotropy. In other words, independent or disparate alterations in aortic diastolic pressure and left ventricular filling pressure can profoundly affect the indexes of inotropy used in this investigation. However, the parallel reduction in left ventricular filling pressure and aortic diastolic pressure resulted in an isovolumic developed pressure that was not different from that in the control period during the entire 8 hour period after administration of either hydralazine or prazosin. In short, hydralazine decreased the preejection period and the time (Δt) required to generate the same isovolumic developed pressure (thereby increasing $\Delta P/\Delta t$), indicating positive inotropy. Prazosin did not alter the preejection period or isovolumic contraction time that, in the face of a constant isovolumic developed pressure, indicates minimal to no inotropic properties.

Role of afterload reduction: Afterload reduction itself may shorten the preejection period and the isovolumic contraction time[9] and, hypothetically, the failure of afterload reduction with prazosin to shorten these intervals may be secondary to concomitant negative inotropic properties. This explanation is not applicable for two reasons. First, the shortening of the preejection period and the isovolumic contraction time with afterload reduction is dependent on decreasing aortic diastolic pressure more than left ventricular filling pressure,[9] which did not occur with either drug. Second, while diminished chronotropic responses have been attributed to prazosin (postsynaptic sympathetic blocking agents)[10] there is no evidence that this drug has negative inotropic properties. Therefore, it is unlikely that the disparate effects of hydralazine and prazosin on the preejection period and the $\Delta P/\Delta t$ are secondary to afterload reduction alone with hydralazine and combined afterload reduction and negative inotropy with prazosin.

Role of ventricular filling pressure: The contractile state of a ventricle is directly related to its end-diastolic size (Frank-Starling phenomenon), which is, in large part, a function of ventricular filling pressure. The mean left ventricular filling pressures of patients treated with hydralazine were not significantly different from those of patients treated with prazosin; therefore the augmented inotropy of hydralazine cannot be explained as differences in ventricular filling pressure (pulmonary capillary wedge pressure). Although hydralazine is not noted for any primary preload-reducing properties, this agent effected a decrease in the pul-

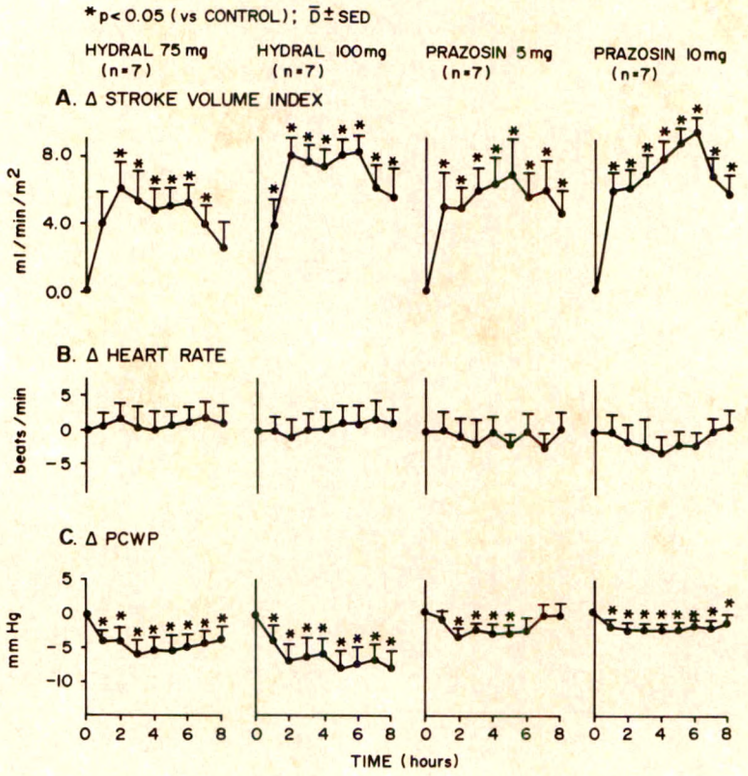


FIGURE 3. A, The responses of stroke volume index to 75 and 100 mg of hydralazine (HYDRAL) were comparable with responses to prazosin at 5 and 10 mg, respectively. **B,** neither drug altered mean heart rate from the control value. **C,** hydralazine, 75 mg, and prazosin, 5 and 10 mg, effected a similar decrease in the pulmonary capillary wedge pressure (PCWP). The 100 mg dose of hydralazine reduced this pressure further. None of the pulmonary capillary wedge pressure response curves were significantly different from each other.

monary capillary wedge pressure in this study; this decrease cannot be attributed to a reduction in mitral regurgitation, because patients with valve regurgitation were excluded from study. Other investigators[11–13] have reported a similar reduction in the pulmonary capillary wedge pressure after hydralazine therapy for congestive heart failure.

Role of ventricular volume changes: Left ventricular end-diastolic volumes were not measured in this study. Although it is unlikely, one cannot absolutely exclude the possibility that left ventricular end-diastolic volume decreased more with prazosin than with hydralazine (despite similar reductions in left ventricular filling pressure), thereby shifting the prazosin points to the left (and lower) of the hydralazine values on the same Frank-Starling function (contractility versus ventricular volume) curve. A recent study[14] in baboons questions the importance of acute ventricular volume changes in controlling the inotropic state of the ventricle.

Mechanisms of hydralazine-induced inotropy: The precise mechanism for this apparent hydralazine-induced inotropy in our patient group is not known. Direct stimulation of the myocardium is the most attractive possibility. It is unlikely that the positive inotropic effect is secondary to reflex activation of the cardiac sympathetic nerves; a positive chronotropic response was not provoked with hydralazine. Although reflex sympathetic activity may not be a major component of hydralazine-induced inotropy, two reported studies[2,15] suggest that hydralazine may directly or indirectly (by way of histamine release) stimulate beta adrenergic receptors. In both studies the local inotropic effect of hydralazine was blocked with beta receptor blocking agents. If hydralazine does act on the myocardium through stimulation of the beta adrenergic receptors, a differential effect on chronotropic and inotropic receptors is implicated. In addition, it is interesting to speculate that the positive inotropic effects of hydralazine may be short-lived with long-term administration secondary to a reduction in number or sensitivity of the beta adrenergic receptors, similar to that seen with long-term catecholamine stimulation. Again, afterload reduction with hydralazine does not account for the improvement of the inotropic indexes; developed pressure was not altered and first dose prazosin elicited a similar increase in stroke volume, and the changes in total systemic resistance effected by the two agents were comparable. Although the underlying mechanisms for the findings of our study have not been precisely delineated, the integration of these mechanisms has resulted in the observation that hydralazine appears to elicit positive inotropy in the failing human ventricle and prazosin does not.

Clinical implications: The positive inotropic properties of hydralazine do not appear to be essential for augmentation of cardiovascular performance; in fact, in certain situations the positive inotropy may be harmful. In patients with congestive heart failure secondary to ischemic myocardium, an agent capable of increasing stroke volume without augmenting inotropy would be preferable. First dose prazosin elicited a comparable increase in stroke volume without increasing ventricular inotropy. Unfortunately, the long-term administration of prazosin is characterized by the development of pharmacodynamic tolerance of resting hemodynamic values.[16–18] The two popular agents, hydralazine and prazosin, may not be ideal vasodilators despite their widespread use. Additional research directed toward the development of an ideal vasodilator is needed.

Acknowledgment

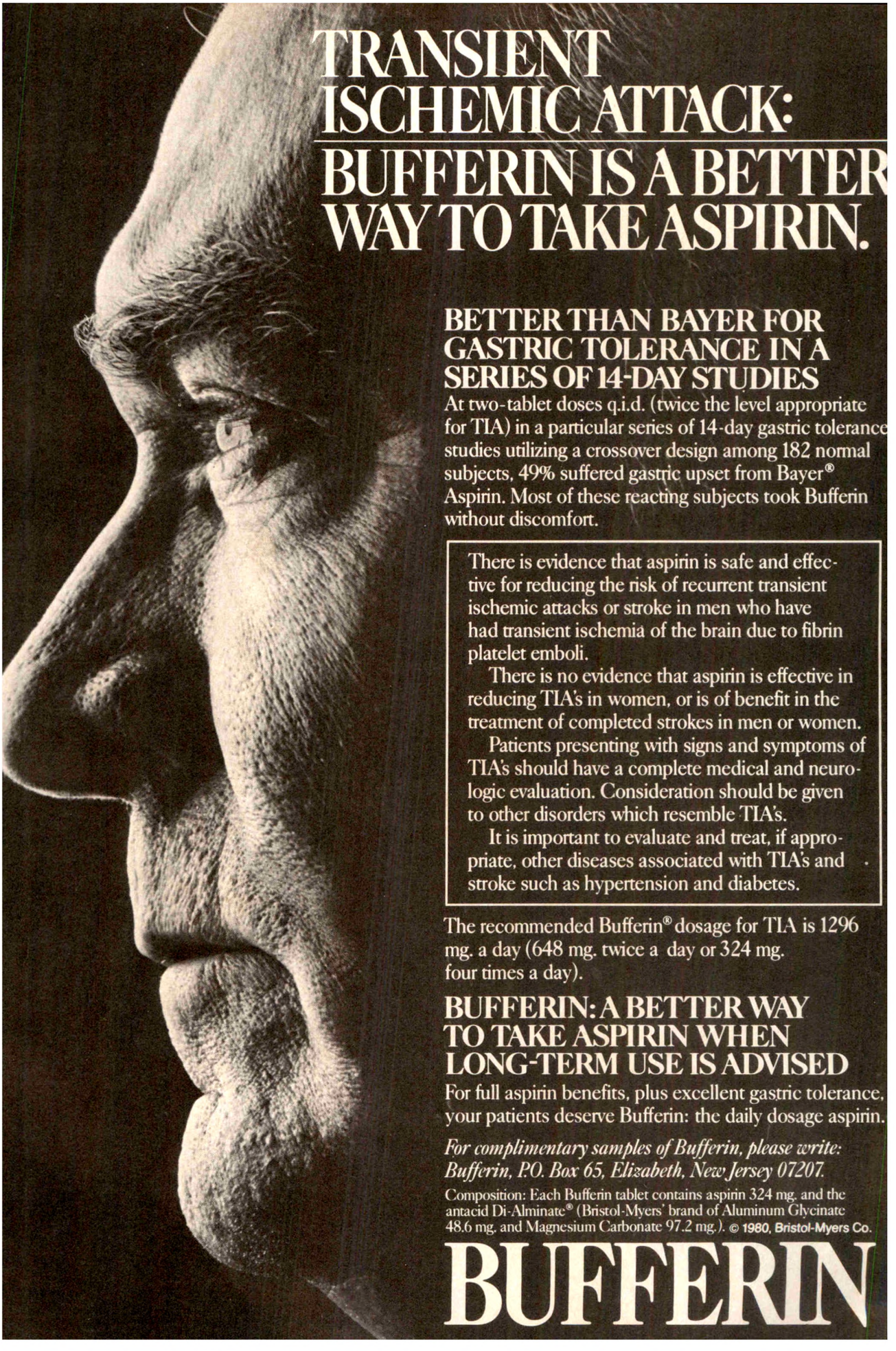
We thank Max Bacher, Mitzi Prosser, Jackie Miller and Patricia Huss for their technical assistance.

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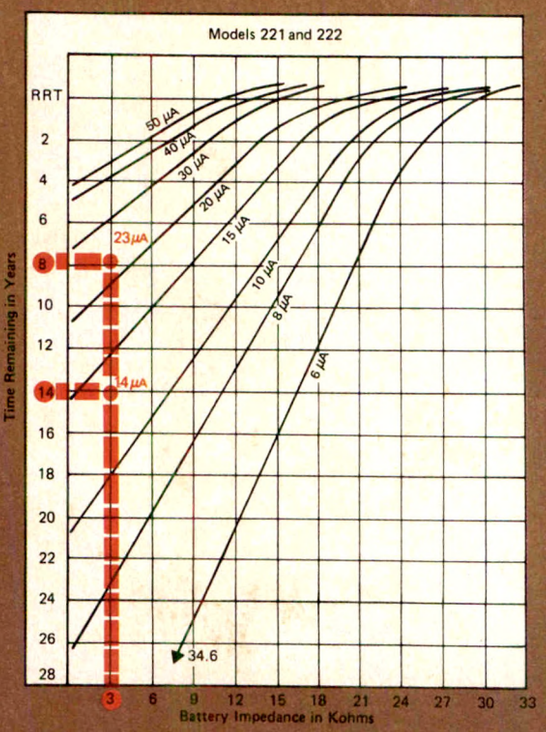
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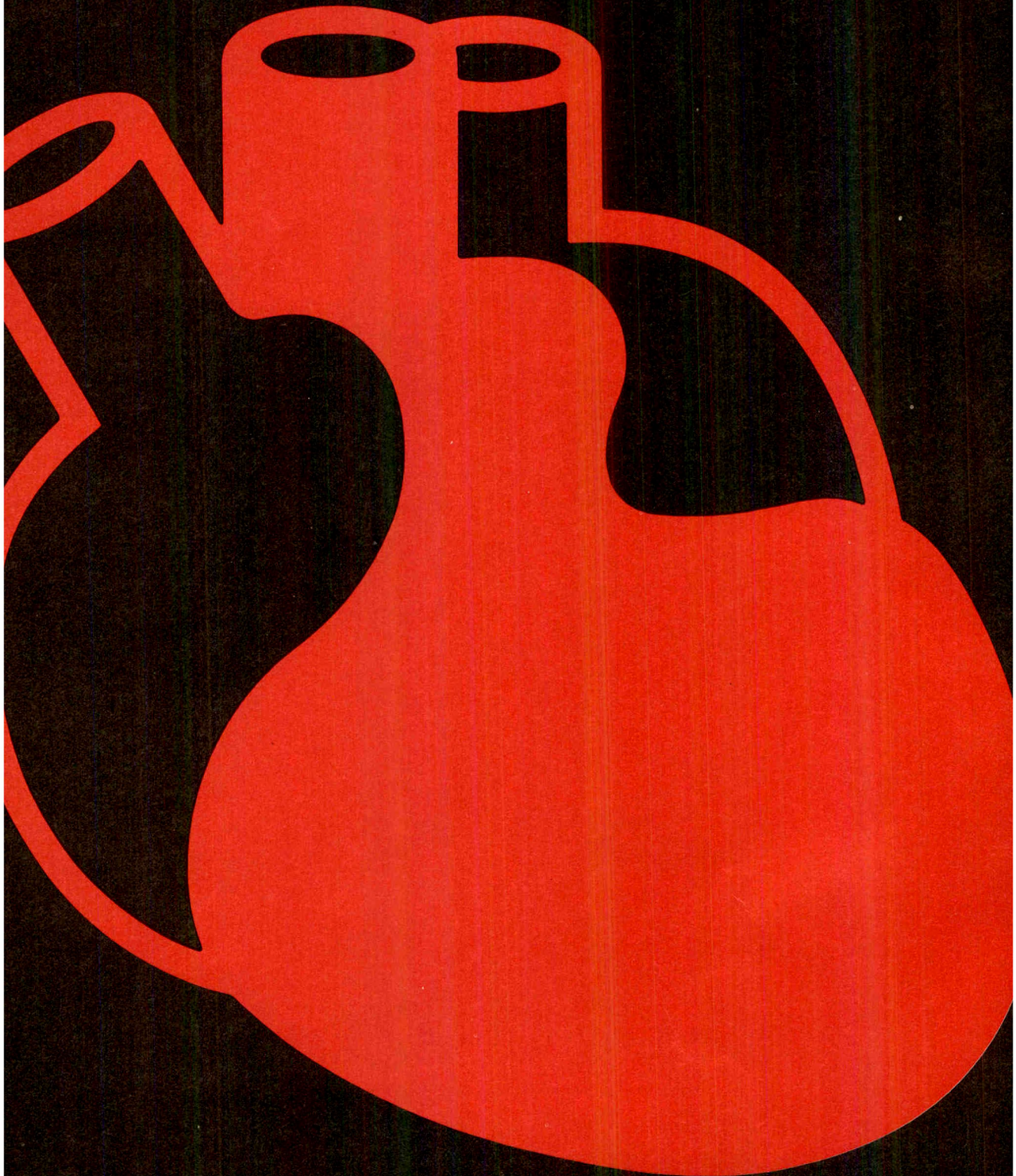
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In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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It is widely recognized that calcium ions (Ca^{++}) play vital roles in many cell processes in a variety of tissues. Ionic calcium is particularly critical to the function of cardiac tissue and vascular smooth muscle. The transition from the resting to the active state in the myocardium is initiated by cell depolarization, which may be recorded as the transmembrane action potential, composed of an initial sharp spike followed by a prolonged plateau. The former is caused by the movement of sodium ions into the cell, whereas the latter results largely—although not entirely—from the inward movement of Ca^{++}. Almost 100 years ago Ringer established the importance of Ca^{++} to cardiac contraction, and it is now appreciated that activation of contraction results from an elevation of the intracellular concentration of Ca^{++} above 10^{-7} M. This, in turn, removes the inhibitory influence of the troponin-tropomyosin complex on the interaction between actin and myosin; actin filaments are displaced relative to myosin filaments and contraction ensues. Thus, the Ca^{++} that enters the cell during the plateau of the action potential plays an essential role coupling myocardial excitation to contraction, although there is evidence that the transmembrane flux of Ca^{++} may merely trigger the release of larger quantities of the ion from intracellular stores and that it is the latter that actually activates the contractile mechanism.

The electrophysiologic properties of specialized cardiac tissue (that is, the automaticity of the sinoatrial and atrioventricular nodes, the velocity of conduction, rhythmicity and excitability of Purkinje fibers) are all profoundly influenced by the intracellular Ca^{++} concentration. Similarly, the extent of contraction of smooth muscle in the systemic and coronary vascular beds is dependent on the entry of Ca^{++} into vascular smooth muscle cells.

Sodium (Na^{+}) and Ca^{++} may be considered to enter the cell through "channels" in the cell membrane, the former through the so-called fast channels and the latter through the slow channels. The magnitude of influx of Ca^{++} into cardiac cells is determined by the number of slow channels that are open and the extent of their opening. The slow channels are "guarded" by two types of gates, one of which is voltage-dependent and is opened by depolarization of the cell to a threshold voltage whereas the extent of opening of the other gate appears to be controlled by activation of a protein kinase by cyclic adenosine monophosphate (AMP). The channels through which the ions enter can be blocked by a variety of drugs that act on these gates. Thus, the fast channels, which the Na^{+} traverses, can be blocked by tetrodotoxin, lidocaine and procainamide. In 1971 Fleckenstein demonstrated that certain pharmacologic agents may interfere with the inward movement of Ca^{++} during the plateau of the action potential. These drugs are properly called *inhibitors* or *blockers* of the slow calcium channels. Their site of action is limited to the cell membrane, but unlike the beta adrenergic receptor blocking agents they *do not* appear to be specific blockers. Again, in contrast to the beta receptor blocking agents, the Ca^{++} channel blockers vary markedly in their chemical structure. Although the molecular basis for the action of these compounds is unknown, because they are lipophylic it appears likely that they produce conformational changes in the cell membranes.

In view of the central role played by Ca^{++} in the electrophysiologic and mechanical prospectives of the heart and the resistance of systemic and coronary arteries, it is not surprising that Ca^{++} channel blockers can produce profound alterations in cardiovascular function. These actions can be taken advantage of in the treatment of a wide variety of cardiovascular disorders that include: (1) a number of cardiac arrhythmias, especially reentrant paroxysmal supraventricular

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tachycardia, but also atrial flutter and fibrillation; (2) angina pectoris, not only chronic stable angina, but also unstable angina and especially Prinzmetal's variant angina in which coronary vasospasm plays a critical etiologic role; (3) arterial hypertension; and (4) hypertrophic obstructive cardiomyopathy. The use of these agents in limiting ischemic damage in patients with acute myocardial infarction and in those who undergo cardiopulmonary bypass has been suggested but has not yet been firmly established. Also, they may be useful as afterload-reducing agents in the treatment of heart failure.

Clinical experience with calcium channel blockers in the United States is limited because they have not yet been approved in this country. However, they have been used extensively and successfully in Europe for a number of years. Although the precise role of these drugs has not yet been defined, it is safe to state, I believe, that the development of calcium channel blockers represents a substantial advance in cardiovascular therapeutics.

This short Seminar on calcium channel blockers is presented in an effort to broaden understanding of this important class of agents. Although the Seminar was not designed to provide a comprehensive and exhaustive description of these drugs it does provide insight into the basic and clinical pharmacology of these compounds, their electrophysiologic properties and their use in various forms of angina pectoris, particularly those varieties secondary to coronary vasospasm.

Comparative Pharmacology of Calcium Antagonists: Nifedipine, Verapamil and Diltiazem

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Calcium antagonists (slow channel blocking agents) are a very heterogeneous group of agents with dissimilar structural, electrophysiologic and pharmacologic properties. Nifedipine is a potent, long-acting vasodilator that has proved highly efficacious in relieving anginal symptoms caused by coronary vasospasm. In vivo, it exerts no myocardial depressant effects and has no antiarrhythmic properties. Treatment with nifedipine can safely be combined with administration of a beta receptor blocking agent. Verapamil prolongs atrioventricular (A-V) conduction (A-H interval) in a dose-dependent manner. It is the drug of choice for the treatment of reentrant supraventricular arrhythmias, irrespective of whether reentry occurs within the A-V node or through an accessory pathway (the Wolff-Parkinson-White syndrome). Verapamil is only moderately effective as an antianginal agent. Diltiazem is efficacious for the treatment of angiospastic angina, but its value as an antiarrhythmic agent remains to be delineated.

In 1960 Lindner[1] observed that prenylamine, a newly developed coronary dilator, depressed cardiac performance in canine heart-lung preparations. Shortly thereafter, Haas and Härtfelder[2] noted that verapamil, another phenylalkylamine with coronary dilating properties, exerted negative inotropic effects on isolated cat and rabbit myocardium. The potent cardiodepressant effects of these new agents appeared to distinguish them from classic vasodilators. Drugs such as nitroglycerin and papaverine are potent smooth muscle relaxing agents, but depress cardiac muscle only at high concentrations, if at all. Because the inotropic and chronotropic effects of prenylamine and verapamil were opposite to those elicited by catecholamines, the new drugs were first thought to be adrenergic blocking agents.[3,4] However, Fleckenstein et al.[5] were among the first to recognize that the effects of prenylamine and verapamil differed from those of beta receptor blockers. They observed that the drugs depressed cardiac contractility without altering the height and contour of the monophasic action potential and concluded that the agents acted as uncouplers of excitation-contraction coupling. The action of the drugs was attributed to an inhibition of the influx of calcium ions (Ca^{++}) into myocardial cells. Consequently, the agents were named "Ca^{++}-antagonists".[5] Later, Fleckenstein[6] specified that Ca^{++} antagonists acted by reversibly sealing specific Ca^{++} channels in the membrane of the mammalian myocardial cell.

In other studies, Grün and Fleckenstein[7,8] applied the principle of electromechanical uncoupling to smooth muscle. In these reports, nitroglycerin was described as a Ca^{++}-antagonistic agent with selectivity for vascular smooth muscle.[7,8] Thus, the term Ca^{++} antagonist was now applied to drugs with little or no direct action on myocardium. Electrophysiologic data supporting the concept of electromechanical uncoupling in vascular smooth muscle were not presented.

After the pioneering studies of Fleckenstein and associates numerous drugs were included among the Ca^{++} antagonists. Some agents such as D 600 (methoxy-verapamil)[4,6] and fendiline (demethyl-prenylamine)[9] were derivatives of the compounds originally studied by Lindner[1] and

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Haas and Härtfelder.[2] However, the majority of the agents tentatively listed as Ca^{++} antagonists were structurally unrelated and appeared to differ in their pharmacologic properties.[10,11] Ca^{++} antagonistic properties were attributed to drugs such as papaverine,[12] diazoxide,[13] perhexiline,[10] lidoflazine,[14] cinnarizine,[15] proadifen (SKF 525 A),[16] diethylaminoethylhexestrol,[14] bencyclane,[14,17] RO 11-1781,[18] nifedipine,[19] diltiazem[20] and molsidomine.[21] Yet, comparative studies[10,11,14] defining the electrophysiologic effects of these compounds were not performed, and consequently it remained undecided whether their mode of action depended predominantly on the mechanism invoked by Fleckenstein. In addition, some investigators[22] began to apply the term Ca^{++} antagonist to agents thought not to block Ca^{++} influx, but to act intracellularly. These authors[23] further broadened the concept of Ca^{++} antagonism and included virtually every smooth muscle relaxing agent among the Ca^{++} antagonists. Thus, local anesthetics, drugs that block the inward movement of sodium (Na^+) rather than that of Ca^{++}, and beta adrenergic agonists, drugs that tend to augment Ca^{++} influx into muscle cells, were paradoxically classified among the Ca^{++} antagonists. As the precise mechanism of action of most agents categorized as Ca^{++} antagonists was not elucidated, the concept of Ca^{++} antagonism remained somewhat vague, and a universally accepted definition failed to emerge.[14]

Mechanism of Action of Ca^{++} Antagonists

Cardiac Muscle

To evaluate the question whether there are drugs that act by selectively blocking specific calcium channels in cardiac membranes, some electrophysiologic concepts will briefly be reviewed (for more detail see Ref. 24 to 26). According to current views,[24,25] cardiac membranes possess ionic channels or aqueous pores that permit ions to move across the sarcolemma. These ionic movements give rise to passive inward (depolarizing) and outward (repolarizing) currents that appear to be responsible for the electrical activity of the heart. The currents are controlled by conformational changes in the channels that determine an all-or-nothing opening of the pores. These conformational changes are usually described as gating. As the gating structures (macromolecules) bear electric charges, conformational changes generate small, nonionic currents referred to as gating currents. Gating mechanisms are sensitive to the electrical field in the membrane and to chemical agents such as neurotransmitters or drugs. Experiments with voltage clamps have demonstrated that there are two distinct inward currents that contribute to the depolarization of cardiac membranes. A brief opening of fast sodium (Na^+) channels is responsible for the initial spike of the action potential, and a subsequent opening of slow channels contributes to the plateau of the action potential. The current flowing through the slow channel is carried by Ca^{++}, but depending on the species and cell type Na^+ may also contribute to this flow. In some normal cells (sinus and A-V nodal cells) and in partly depolarized contractile cells, a rapid spike is absent and depolarization appears to occur predominantly through the slow channel ("slow response").

One classic model[24] *for the description of the behavior of the depolarizing inward currents* has been to assume that the fast and slow channels are each controlled by two gating mechanisms located in series along the channels (Hodgkin-Huxley model). According to this scheme, the outer and inner gates control the activation and inactivation of the currents, respectively. At rest, the outer activation gate is closed, whereas the inner inactivation gate is open. With depolarization, the outer gate opens ("activation"), leaving both gates momentarily open and permitting ions to flow through the channel. However, with some delay, the inner gate closes, interrupting the flow of current ("inactivation"). Thereafter, there is a period of recovery during which the outer gate closes and the inner gate subsequently reopens ("recovery from inactivation," "reactivation," "restoration"). During this period of recovery, a repeat depolarization elicits only diminutive responses, a phenomenon that may be explained by assuming that not all of the inner gates have reopened yet.

At least four different repolarizing outward currents have been distinguished in Purkinje fibers.[24,25] These late or delayed currents are carried predominantly by potassium ions. Potassium (K^+) channels are controlled with activation gates, but in contrast to the fast and slow channels do not appear to possess independent inactivation mechanisms.[24] The effects of Ca^{++} antagonists on K^+ channels have not been analyzed in detail, and outward currents will not be discussed here. However, one mechanism influencing outward currents deserves to be mentioned. There is evidence that the intracellular Ca^{++} concentration ($[Ca]_i$) regulates K^+ conductance.[27] Increasing $[Ca]_i$ causes an increase in the late outward current of sheep Purkinje fibers.[27] Therefore, an inhibited cellular Ca^{++} uptake leading to a decreased $[Ca]_i$ may be anticipated to reduce the late outward current.

One major argument supporting the membrane pore theory is the discovery that drugs may selectively inhibit specific currents.[28] Thus, tetrodotoxin and local anesthetic agents such as lidocaine exert inhibitory effects on the fast current without appreciably affecting the slow current.[24,26] However, the mechanism of action of tetrodotoxin and of local anesthetics appear to differ substantially. There is considerable evidence that tetrodotoxin and related cationic compounds insert themselves into the outer opening of the fast channels, thereby physically blocking ion flow through the channel. Tetrodotoxin does not appear to affect the deeper portions of the channel, and the gating machinery (gating currents) remains unaltered.[26] However, a local anesthetic such as lidocaine blocks the sodium channels from the inner surface of the membrane.[29] The drug appears to immobilize gating charge movements and to slow the kinetic parameters of the current.[26] These effects are manifested by a decrease in the maximal rate of depolarization (activation) and in a delayed recovery of the sodium conductance (reactivation).

However, lidocaine may have more than one site of action in canine Purkinje fibers, and its effects may not be limited to the fast Na^+ channel. In particular, the drug is known to increase the potassium conductance of Purkinje fibers.[29] Another interesting feature is that the action of local anesthetic agents appears to depend on the rate of stimulation (that is, the blockade of the Na^+ channel may be small under quiescent conditions, but may be markedly enhanced after a rapid train of depolarizations).[26] Because local anesthetic agents do not act exclusively on the fast Na^+ channels, and because tetrodotoxin and local anesthetic agents do not act by a single electrophysiologic mechanism, little would be gained by placing these drugs in a single category of "Na^+ antagonists."

The first agents shown to inhibit the slow inward current without influencing the fast depolarization were metallic ions such as manganese (Mn^{++}),[30] nickel (Ni^{++})[24] and cobalt (Co^{++}).[24] The mechanism of action of these divalent cations is complex and will not be reviewed here (for more detail see Ref. 24). However, one important mechanism should be mentioned. In cardiac muscle, a coupled exchange mechanism involving the exchange of two Na ions for one Ca ion has been described.[31] Thus, in contrast to the electrogenic slow inward current described, this exchange is electroneutral and cannot be detected with electrophysiologic techniques. It has been suggested that Na^+/Ca^{++} exchange may play an important role in providing activator Ca^{++} for the contractile apparatus of the myocardial cell.[32] Thus, cardiodepressant effects of metallic cations may reflect not only a blockade of the slow inward current but also a displacement of superficially located Ca^{++} participating in the Na/Ca^{++} exchange.[32]

In the light of the electrophysiologic concepts outlined, results of electrophysiologic experiments with nifedipine, verapamil and D 600 (methoxy-verapamil) will briefly be discussed.

Nifedipine: Kaufmann[14] Bayer et al.[33,34] and Ehara and Kaufman[35] have investigated the effects of nifedipine on the membrane currents of cat papillary muscle under voltage-clamp conditions. Nifedipine (10^{-7} to 10^{-5} *M*) did not influence the fast Na^+ inward current, but depressed the slow inward current in a dose-dependent manner. The drug had no apparent effect on the kinetic parameters of the slow current (rate of activation and inactivation), and did not delay the recovery from the inactivation (refractoriness after slow response). Nifedipine consistently increased the delayed potassium outward current. Effects of nifedipine were not influenced by rate changes between 6 and 60/min. In similar experiments with cat papillary muscles, Kohlhardt and Fleckenstein[36] found nifedipine not to affect the rate of inactivation of the slow current or to prolong the period of recovery. These findings indicate that nifedipine has no local anesthetic (Na^+ channel blocking) properties and inhibits the slow inward Ca^{++} current without altering the kinetic control mechanisms (gating mechanisms) of the slow channels. The action of nifedipine on the slow channels resembles that of tetrodotoxin on the fast channels. One may assume that nifedipine prevents the activation of some of the slow channels, leaving the rest of the slow channels and their time-dependent gating mechanisms unaffected. However, additional experiments are needed to determine whether nifedipine obstructs the outer pore of the slow channels.

Verapamil and D 600: Experiments with isolated cardiac muscle have shown that the optical isomers of verapamil and D 600 exert disparate electrophysiologic effects.[14,37–40] The (R) (+)-enantiomers (9×10^{-6} *M*) of the two drugs depress appreciably the maximal rate of rise of the monophasic action potential at a frequency of 15/min, and this effect is markedly enhanced at a frequency of 90/min. However, in equal concentration, the (+)-isomers appear to have modest effects on the plateau phase and overall shape of the action potential.[37] In contrast, the S(−)-enantiomers (9×10^{-6} *M*) depress the plateau phase of the action potential in a frequency-dependent manner.[37] These findings suggest that the (R+)-enantiomers have a substantial fast channel blocking (local anesthetic) activity, whereas the (S)(−)-enantiomers predominantly affect the plateau of the action potential, a change compatible with a blockade of the slow current. This interpretation is supported by the observation that the (+)-isomers mainly depress excitability, whereas the (−)-isomers are responsible for the negative inotropic effects of the racemic mixtures.

Voltage-clamp experiments with cat papillary muscles confirmed that (−)-verapamil in concentrations ranging between 8×10^{-7} and 2.2×10^{-7} *M* suppresses the slow inward current in a frequency-dependent manner.[38] Similarly, (±)-D 600 (10^{-7} to 10^{-6} *M*) has been reported to inhibit the slow inward current in feline ventricular myocardium[41,42] and bovine Purkinje fibers.[43] Effects of verapamil and D 600 are markedly enhanced by prolonged incubation.[38,41,43] Thus, the inhibitory effects of these compounds strongly depend on the rate of stimulation and on the length of exposure to the drugs. In contrast to nifedipine, verapamil and D 600 alter the kinetics of the slow current. The agents slow down activation and more prominently the recovery from inactivation.[14,38,42,44] The prolongation of the recovery of the slow channel revealed by voltage clamp experiments appears to be an important electrophysiologic effect of verapamil, as it provides a potential explanation for the efficacy of the drug in terminating reentrant tachyarrhythmias. (−)Verapamil[38] and (±)D 600[41,43] have also been noted to decrease the delayed potassium outward current(s). As indicated, a decreased $[Ca]_i$ resulting from an inhibited Ca^{++} influx might secondarily reduce the delayed potassium outward current.[27] In some instances, (−)verapamil[38] and (±)D 600[41,43] have been found to reduce the outward currents, but this effect has been variable.[38,43] In some instances, the outward current may increase instead. Furthermore, it does not appear that decreases in the outward current result simply from the inhibition of the slow inward current.[43]

Thus, the effects of (±)*-verapamil and* (±)*-D 600 appear to be quite complex.* First, the action of the drugs are a sum effect of optical isomers possessing different electropharmacologic properties. Second, the effects of the drugs are markedly frequency-dependent and become fully manifest only after prolonged incubation. Third, in addition to inhibiting the slow inward current and altering its kinetic properties, the drugs affect the delayed outward current(s) and (at high concentrations) the fast inward current. It is evident that verapamil is not a selective blocker of the slow inward current. In some respects, the action of verapamil on the slow channel resembles that of lidocaine on the fast channel. Both drugs appear to affect the time-dependent gating mechanisms and markedly retard channel recovery (reactivation). In addition, the drugs exhibit the phenomenon of frequency dependence. It would be interesting to determine whether verapamil, like lidocaine, acts from the inside of the sarcolemma.

The demonstration that nifedipine, verapamil and D 600 block the slow inward current supports, in part, Fleckenstein's original hypothesis.[6] However, current information indicates that these drugs differ substantially in their mechanism of action. Nifedipine appears to be a more selective slow channel blocker than are verapamil and D 600. Voltage clamp experiments provide no information on the carrier-mediated, electroneutral Ca^{++}/Na^{+} exchange which may play an important role in activating cardiac muscle.[32] Little is known about the nature of the coupled exchange mechanism, and there is no information concerning the effects of Ca^{++} antagonists on this system. Thus, it would be premature to make definitive conclusions regarding the dominant mechanism of action of drugs with Ca^{++} antagonistic effects.

Diltiazem: Diltiazem (2.2×10^{-6} *M*) lowers the plateau and shortens the duration of the monophasic action potential of canine Purkinje fibers.[45] In canine ventricular myocardium, diltiazem (2.2×10^{-6} *M*) lowers the plateau and at the same time depresses contractility.[45] High concentrations (2.2×10^{-5} *M*) reduce the maximal rate of rise of the monophasic action potential of canine Purkinje fibers,[45] guinea pig atria[46] and guinea pig ventricular myocardium.[47] These findings suggest that diltiazem may block the slow current at low concentrations and exert fast channel inhibitory effects at high concentrations. Voltage clamp experiments with diltiazem have not been reported.

Vascular Smooth Muscle

There is little detailed information regarding the mechanism of action of Ca^{++} antagonists on vascular smooth muscle. Harder et al.[48] studied the effects of (±)verapamil on Ca^{++} dependent action potentials in isolated large (more than 1 mm) and small (less than 0.5 mm) canine coronary arteries. In these vessels, spontaneous action potentials or action potentials in response to electrical stimulation, are not observed. However, electrical stimuli evoke "Ca^{++}-spikes" in the presence of 10 m*M* tetraethyl ammonium ions (TEA), an intervention that acts by suppressing the K^{+} outward current and reducing the rectifying properties of the membrane. TEA-facilitated, Ca^{++}-dependent action potentials were blocked by 10^{-6} *M* (±)verapamil in both large and small vessels. Adenosine (10^{-5} *M*) blocked the spikes only in small vessels, whereas nitroglycerin (10^{-5} *M*) was selective for large vessels.[48] In fibrillating arterially perfused canine hearts, verapamil and nifedipine were reported to relax only small resistive arteries and arterioles, whereas nitroglycerin preferentially relaxed large (conductance) coronary arteries.[49]

Thorens and Haeusler[18] exposed isolated rabbit pulmonary arteries to selected vasodilators in the presence of 50 m*M* of potassium chloride (KCl) and 2.2 m*M* of calcium chloride ($^{45}CaCl_2$). After a subsequent 1 hour wash with 1 m*M* of lanthanum trichloride ($LaCl_3$), tissue-bound radioactivity was measured as an index of "Ca influx." (±)Verapamil, RO 11-1781 and papaverine produced dose-dependent inhibitions of ^{45}Ca influx. Nitroglycerin, diazoxide and nitroprusside exerted little or no inhibitory effects. Results were interpreted to indicate that only verapamil, RO 11-1781 and papaverine may cause vasorelaxation by interfering with Ca^{++} influx.[18]

Massingham[50] and Nguyen Duong and Brecht[51] demonstrated in isolated vessels that (±)verapamil, (±)D 600 and nifedipine relaxed KCl-induced contractures more effectively than contractions evoked by norepinephrine. The efficacy of Ca^{++} antagonists in relieving KCl contractures are thought to reflect the fact that K^{+} evokes contractions indirectly by promoting vascular Ca^{++} uptake.[18,50,51] In agreement with this concept is the observation that bovine coronary arteries contracted by fluoride ions, a contracture thought to be independent of extracellular Ca^{++}, are not effectively relaxed with verapamil and prenylamine.[52] Interestingly, these contractures appear to be readily relaxed with nitroglycerin and nitroprusside.[52] Mikkelsen et al.[53] reported that in isolated human mesenteric arteries and veins, verapamil is equally potent in relieving contractions induced by KCl and norepinephrine, a finding that appears to be in conflict with the studies mentioned.[50,51]

Studies with isolated arteries and veins generally confirm the view that the relaxing effects of verapamil and nifedipine differ from those of classic vasodilators such as nitroglycerin and nitroprusside. They strongly suggest that Ca^{++} antagonists act partly by blocking the inward movement of Ca^{++} into smooth muscle cells. However, experiments demonstrating the inhibition of "Ca-spikes" and ^{45}Ca uptake were performed in the presence of abnormal ionic conditions.

Structure of Ca^{++} Antagonists

The subsequent discussion will focus on nifedipine, (±)-verapamil and diltiazem, the agents currently receiving the most clinical attention.

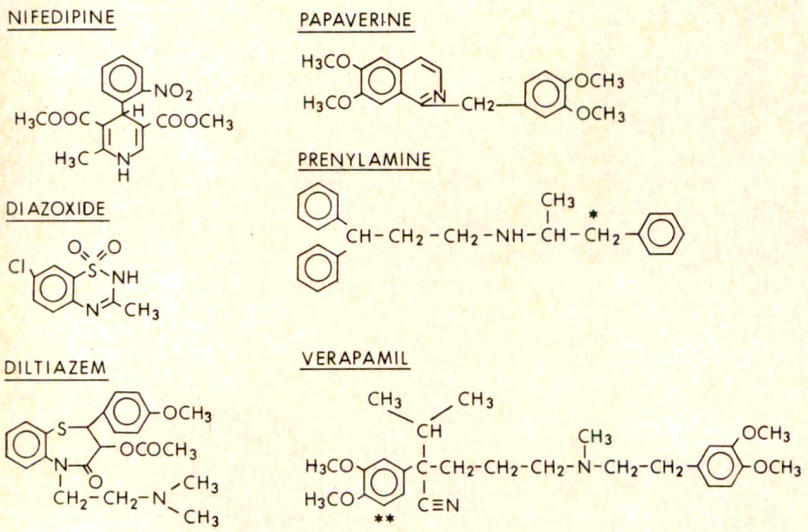


FIGURE 1. Chemical structure of calcium antagonists and other vasoactive drugs.

Nifedipine: Nifedipine (BAY a 1040; MW 343) is a dihydropyridine derivative that bears no structural similarity with other already known vasoactive or cardioactive drugs (Fig. 1).[19] Nifedipine is not a nitrate, and its ortho NO_2 group is not essential for its pharmacologic activity.[54] Multiple dihydropyridine derivatives have been synthetized and some (niludipine and nimodipine) are receiving investigative attention.

Verapamil: (±)-Verapamil (D 365, Iproveratril, Isoptin and MW 455) has some structural features in common with papaverine (Fig. 1). Compared with verapamil, D 600 has one more methoxy group attached to the benzene ring close to the asymmetrical C-atom.[2,4,55]

Diltiazem: Diltiazem (CRD 401; MW 450) is a benzothiazepine derivative that is structurally unrelated to diazoxide (a benzothiadiazine derivative) (Fig. 1).[20]

Pharmacokinetics of Ca^{++} Antagonists

Nifedipine: The pharmacokinetics of nifedipine in human beings were studied with ^{14}C-nifedipine in conjunction with chromatographic and mass spectrometric analyses[56,57] (Table I). More than 90 percent of nifedipine is absorbed after oral administration. Only approximately 20 to 30 percent of nifedipine is removed from portal blood by the liver, yielding a systemic availability (bioavailability) of more than 65 percent. Bioavailability is a measure of the fraction of the dose reaching the systemic circulation, and is defined as the ratio of the area under the plasma concentration-time curve after oral administration to that obtained after intravenous administration of the same amount of drug. In the case of nifedipine, 15 μg/kg, intravenously, produces approximately the same concentration-time curve as 150 μg/kg orally or sublingually.[56] The main metabolic pathway consists of an oxidation to a "free acid," a small fraction of which is converted to a lactone.[57] These metabolites are pharmacologically inactive. Intact nifedipine is 90 percent bound to plasma proteins, whereas the "free acid" is only 54 percent bound.

The biexponential analysis of the disappearance of nifedipine in plasma yields an initial fast half-life ($T_{1/2}\ \alpha$) of 2.5 to 3 hours and a terminal slow half-life ($T_{1/2}\ \beta$) of 5 hours. Seventy to 80 percent of the radioactivity administered is excreted in the urine, and approximately 90 percent of the urinary excretion occurs during the first 24 hours. Only trace amounts of intact nifedipine appear in the urine. Some of the radioactivity excreted in the bile is reabsorbed (enterohepatic circulation). Only about 15 percent of the radioactivity is recovered in the feces. There is no evidence that metabolites accumulate in the body during long-term administration (for more detail see Ref. 57).

Verapamil: The pharmacokinetics of (±)-verapamil in human beings were studied with radioactive (^{14}C-verapamil), chromatographic and mass spectrometric techniques[58–60] (Table I). Absorption after oral administration varies from 88 to 92 percent. The low bioavailability of verapamil (10 to 22 percent) is due to extensive first pass metabolism in the liver. After oral administration of ^{14}C-verapamil, plasma levels of radioactivity and verapamil (assayed by gas chromatography/mass spectrometry) peak within 30 to 45 minutes. Thereafter, the levels decline biexponentially with fast and slow half-lives of 18 to 35 and 170 to 440 minutes, respectively.[58] Intact verapamil is 88 to 92 percent protein-bound. The drug is extensively metabolized, and 1 to 2 hours after oral administration of ^{14}C-verapamil only about 15 percent of the plasma radioactivity represents intact verapamil.[58] A fluorometric assay of verapamil yields spuriously high drug levels, probably because it measures metabolites as well.[60,61]

The metabolism of verapamil is complex. Cleavage of the C—N—C bond by N-alkylation, preferentially at the C-atom belonging to the shorter side chain, appears to be a major metabolic step. The pharmacologic activity of the cleavage products is only 5 to 10 percent that of verapamil. As cleavage products are formed in large amounts and as their half-lives are long (~24 hours), their plasma concentration during long-term treatment exceeds that of intact verapamil.[58,59] Therefore, it is possible that metabolites contribute to the action of verapamil. Between 67 and 71 percent of the radioactivity after oral ^{14}C-verapamil is excreted in the urine within 5 days. Only 3 to 4 percent of the dose appears as unchanged drug in the urine.[59]

Diltiazem: There is surprisingly little information on the pharmacokinetics of diltiazem. Data shown in Table I are based on studies in dogs.[62] Diltiazem is extensively metabo-

TABLE I

Pharmacokinetics of Calcium Antagonists

	Nifedipine	(±) Verapamil	Diltiazem
Dosage			
Oral (mg/8 h)	10–20	80–160	60–90
Intravenous (μg/kg)	5–15	150	75–150
Absorption			
Oral (%)	>90	>90	>90
Bioavailability (%)	65–70	10–22	<20
Onset of action			
Sublingual (min)	3	...	...
Oral (min)	<20	<30	<30
Therapeutic plasma concentration (ng/ml)	25–100 (7×10^{-8}–2×10^{-7} *M*)	15–100 (3.2×10^{-8}–2×10^{-7} *M*)	30–130 (7×10^{-8}–3×10^{-7} *M*)
Protein binding (%)	90	90	80
Plasma half-time			
Initial fast (α) (min)	150–180	15–30	20
Slow (β) (h)	5	3–7	4
Metabolism	Extensively metabolized to an inert free acid and lactone	Extensive 1st pass hepatic extraction (70% of oral dose)	Extensively deacetylated
Excretion			
Renal (%)	70 1st day (80 total)	50 1st day (70 total)	35 (total)
Fecal (%)	<15	15	65

lized by deacetylation, N-demethylation and O-demethylation.

Cardiovascular Effects of Ca^{++} Antagonists

Nifedipine,[7] (±)-verapamil[6] and diltiazem[46] exert potent negative inotropic effects on isolated myocardium. In contrast, therapeutic doses of these agents do not appear to appreciably depress the heart in the intact organism.[63–66] This seeming paradox has often been attributed to reflex sympathetic discharge masking the direct negative inotropic action of the drug.[63–66] However, negative inotropic threshold concentrations for nifedipine,[34,67,68] (±)verapamil[37,55] and diltiazem[46,47] in vitro are approximately 2×10^{-7} *M*, 5×10^{-7} *M* and 10^{-6} *M*, respectively. These concentrations exceed by a factor of 10 or more peak therapeutic plasma levels of free drug (drug not bound to protein) shown in Table I. In addition, nifedipine, verapamil and diltiazem are all quickly and extensively metabolized, and the full effect of the drugs may develop slowly.[38,41,43] Thus, based on these quantitative considerations, there is no strong reason why Ca^{++} antagonists in usual therapeutic doses should exert potent negative inotropic effects. This is not to indicate that vasodilator-induced arterial hypotension may not trigger a sympathetic discharge. Although Ca^{++} antagonists may inhibit Ca^{++} dependent secretory processes,[9,23] exocytosis of norepinephrine from sympathetic nerve endings is not inhibited by clinically relevant concentrations of verapamil[69] and nifedipine.[70] As nifedipine, verapamil and diltiazem exert disparate effects in vivo, their action will be discussed separately.

Nifedipine

Vasodilator effects: Nifedipine is a potent vasodilator that promptly relaxes isolated arteries contracted by KCl, norepinephrine, serotonin and cardioactive glycosides.[7,9,51] It is in general about as potent as nitroglycerin, but in contrast to nitrates the induced relaxations are sustained. Concentrations as low as 10^{-9} *M* relax pig coronary arterial strips.[9] Isolated human mesenteric arteries and veins contracted by KCl and norepinephrine are relaxed by slightly higher concentrations.[53]

In a study on conscious dogs, nifedipine, 0.43 mg/kg sublingually, decreased total peripheral resistance by 43 percent and mean coronary resistance by 38 percent, but did not produce an appreciable reduction in aortic mean pressure (−6 percent).[71] Heart rate and cardiac output increased by 62 percent, and the maximal first derivative of left ventricular pressure (dP/dt) was augmented by 16 percent.[71] In dogs anesthetized with pentobarbital, hypotensive doses of nifedipine (150 to 1000 μg/kg sublingually) increased coronary flow, whereas, equipotent hypotensive doses of nitroglycerin decreased coronary flow.[72] Nifedipine-induced increases in coronary flow were associated with increases in inferior caval flow ("venous return") and pulmonary arterial flow (cardiac output). In contrast, nitroglycerin tended to reduce venous return and cardiac output.[71] In the isolated blood-perfused canine heart, nifedipine as a coronary dilator was equipotent compared with nitroglycerin, but more potent than dipyramidol, carbochromen, verapamil, prenylamine, papaverine and khellin.[71] Infused into the renal artery, nifedipine abolished renal autoregulation.[71]

Hemodynamic effects of nifedipine in human beings resemble those observed in dogs (for more detail see Ref. 64). In five healthy volunteers, nifedipine, 15 μg/kg intravenously, evoked increases in heart rate (±27 percent), modest decreases in systolic and diastolic arterial pressure, decreases in peripheral resistance (−20 percent) and increases in cardiac index (+40 percent).[73] In seven patients undergoing cardiac catheterization for coronary artery disease, nifedipine, 20 mg sublingually, produced increases in heart rate (+21 percent), cardiac output (+25 percent), and maximal dP/dt (+13 percent). Total peripheral resistance declined (−17 percent). Other measured variables including mean aortic pressure, left ventricular end-diastolic volume index, ejection fraction and mean circumferential shortening velocity did not change significantly.[63,74] Myocardial perfusion assessed in 10 patients by a xenon perfusion scanning technique revealed increased perfusion of normally perfused and underperfused segments after intracoronary injection of 100 μg of nifedipine.[74] After 20 mg of nifedipine sublingually, improved perfusion of normal zones and of zones supplied by stenotic coronary arteries was further documented by thallium scintigraphy.[74] These clinical observations indicate that nifedipine augments coronary flow in human beings.

Electrophysiologic effects: High concentrations of nifedipine (10^{-6} *M*), in sharp contrast to (±)-verapamil, fail to reduce the excitability of isolated guinea pig atria.[75] In conscious dogs, verapamil prolongs the P-R interval,[75,60,61] whereas nifedipine in equally hypotensive doses produces moderate, dose-dependent P-R shortening.[75] Injection of large doses (up to 30 μg) of nifedipine into the posterior septal artery of dogs (the artery supplying the upper A-V nodal area) evokes dose-dependent increases in A-V conduction time.[76] However, increases in blood flow through the posterior septal artery requires only 1/10 the dose necessary to affect A-V conduction. In contrast, with verapamil increase in flow and prolongations in A-V conduction occur within the same dose range.[76]

In a study of 11 patients nifedipine, 7.5 μg/kg intravenously, did not affect the A-H and H-V intervals of the His bundle electrogram.[77] With a hypotensive dosage of 0.15 mg/kg intravenously (±)-verapamil produced in the same subjects dose-dependent prolongations of the A-H interval.[77] The lack of a tendency of nifedipine to precipitate A-V block is an essential feature of this drug, as it permits its safe combination with beta receptor blockers and digoxin,[78] and it may be administered to patients with potential conduction disturbances (bradytachycardia syndrome).[11] The electrophysiologic properties of nifedipine explain in part the lack of antiarrhythmic activity of the drug.[79]

Negative inotropic effects: Nifedipine in usual clinical dosage has little tendency to depress the heart.

On the contrary, the drug tends to increase left ventricular dP/dt and cardiac output, as indicated earlier.

Verapamil

Vasodilator effects: (±)-Verapamil is a potent vasodilator, although its smooth muscle-relaxing effects are weaker than those exerted by nitroglycerin and nifedipine.[7,9,53] In open chest dogs administration of verapamil yielding plasma levels of less than 150 ng/ml (fluorometric assay) produced little hemodynamic change. However, in large doses (bolus injections of 14 to 22 mg, plasm levels as high as 2,000 ng/ml) verapamil induced marked decreases in arterial pressure, heart rate, left ventricular dP/dt, peripheral resistance and cardiac output.[61] However such large doses are not used clinically.

In seven healthy subjects, (±)-verapamil, 7.5 to 12.5 mg intravenously increased heart rate (+14 percent) and cardiac index (+24 percent), and decreased peripheral resistance (−33 percent), mean aortic pressure (−15 percent) and mean pulmonary pressure (−11 percent).[65] Changes in heart rate, cardiac index and peripheral resistance were statistically significant. One patient had 2° A-V block (Mobitz), and three others exhibited prolongation of the P-R interval.[65]

Electrophysiologic effects: In the aforementioned study in open chest dogs,[61] small dose verapamil (plasma level less than 150 ng/ml) prolonged the P-P interval from 397 to 442 ms, and the A-H interval (His bundle electrogram) from 65 to 94 ms. At higher drug levels (less than 400 ng/ml), the P-R and A-H intervals increased to 554 and 136 ms, respectively. Fifty percent of the animals had second or third degree A-V block. The QRS duration, Q-T interval and H-V intervals were not affected even at the highest plasma drug levels (400 to 2,000 ng/ml). Similar dose-dependent prolongation of the P-R interval in dogs have been reported by other investigators.[75]

Therapeutic doses of (±)-verapamil (10 mg intravenously: 120 mg orally) evoke in patients plasma level dependent prolongations of the P-R interval.[60] Furthermore, 0.15 mg/kg verapamil intravenously prolongs the A-H interval without altering the H-V interval.[77] Because of its tendency to produce A-V block, verapamil should be used cautiously in patients in whom A-V block is apt to develop (patients taking digitalis or those with a possible bradytachycardia syndrome) and should not be administered to patients treated with beta adrenergic blocking agents.[11]

Inotropic effects: Compared with nifedipine, verapamil has a greater propensity to exert direct myocardial depressant effects. Nevertheless, in antiarrhythmic doses, precipitation of cardiac failure is unusual.[80]

Diltiazem

Vasodilator effects: In 20 patients undergoing cardiac catheterization for coronary disease or hypertension,[66] hemodynamic findings at rest were monitored before and after 60 mg of diltiazem orally. The drug produced small decreases in heart rate (−6.2 percent) systolic aortic pressure (−9.1 percent), cardiac index (−5.2 percent) and peripheral resistance (−4.1 percent). In two patients undergoing cardiac catheterization for anginal symptoms,[81] an intravenous drip of diltiazem (1 mg/min) evoked negligible hemodynamic changes. Long-term treatment in 20 patients with diltiazem, 90 mg every 8 hours,[81] was interpreted as having led to a significant decrease in cardiac output.

Electrophysiologic effects: Like verapamil, but unlike nifedipine, diltiazem possesses antiarrhythmic effects (for more detail see Ref. 45). This vasodilator has the unusual property of producing no tachycardia or minimal sinus bradycardia.[66]

Comparative Direct Cardiac Effects of Nifedipine, Verapamil, Diltiazem and Other Vasodilators

Direct myocardial effects of vasodilators in vivo are notoriously difficult to evaluate, because vasodilator responses may affect major determinants of cardiac performance including heart rate, ventricular preload, ventricular afterload and coronary flow. Therefore, direct myocardial effects of these drugs are more easily assessed in vitro.

Figure 2 depicts experiments with isolated right guinea pig atria.[82] The atria were mounted so as to contract isometrically in a muscle bath containing oxygenated Krebs buffer. Force (F) development and its first derivative, dF/dt, were monitored before and during the cumulative addition of drug to the buffer. Changes in spontaneous rate and changes in dF/dt during electrical pacing (200/min) served as indexes of chronotropy and inotropy, respectively. Spontaneous frequency and dF/dt at fixed rate were expressed as percent decrease of the control value (=100 percent) before addition of a drug.[82]

Figure 2 shows the responses to selected vasodilators, all administered to produce a drug concentration of 10^{-6} M. Each data point represents a mean ± standard error of the mean in five to six experiments. Verapamil, D 600, and to a lesser extent prenylamine and perhexiline, were effective in depressing both frequency and dF/dt. However, diltiazem acted predominantly on frequency ("chronoselectivity"), and nifedipine predominantly on dF/dt ("inoselectivity"). In sharp contrast, classic vasodilators (papaverine, nitroglycerin, nitroprusside and diazoxide) exerted no or negligible depressant effects on chronotropic or inotropic properties at the 10^{-6} *M* level.

As indicated, the definition of the term Ca^{++} antagonist is somewhat vague. I believe that if one wants to use the term it should be applied only to those vasodilators that depress the heart at low (10^{-6} *M* or less) concentrations. This definition eliminates drugs such as diazoxide and nitroglycerin, vasodilators that do not appear to inhibit Ca^{++} uptake by vascular smooth muscle.[18] Thus, Ca^{++} antagonists may be thought of as drugs which act in vitro as potent "cardiovasodepressants." Such a definition avoids making assumptions about electrophysiologic mechanisms.

Therapeutic Effects of Ca^{++} Antagonists

Although Ca^{++} antagonists have been used clinically mainly as antianginal and antiarrhythmic agents, these drugs may be of value for the treatment of other disease

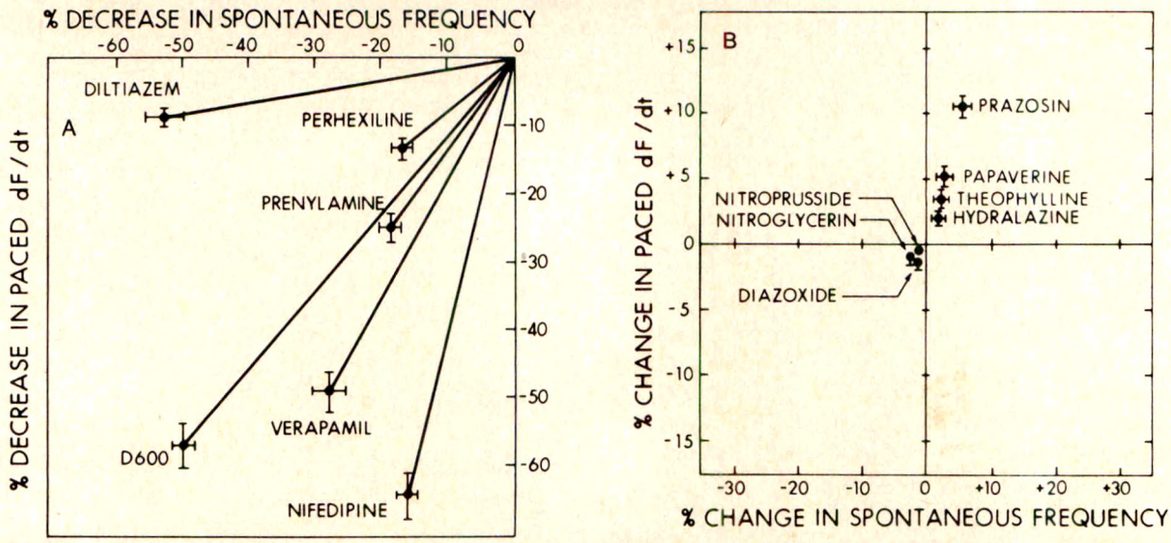


FIGURE 2. Responses of first derivative of force development (dF/dt) during electrical pacing and of spontaneous rate (frequency) of isolated guinea pig atrium to selected vasodilators all administered to produce a drug concentration of 10^{-6} *M*. **A**, selected vasodilators including calcium antagonists. **B**, classic vasodilators.

states. Treatment with Ca^{++} antagonists have been recommended or proposed for the following conditions:

1. Angiospastic angina (Prinzmetal's angina)
2. Angina pectoris, any type
3. Arrhythmias
4. Arterial hypertension
5. Left ventricular failure (vasodilator therapy)
6. Acute myocardial infarction
7. Cardiac preservation (cardiac surgery)
8. Cardiomyopathy
9. Cerebral vasospasm
10. Other vasospastic syndromes

The value of nifedipine, verapamil and diltiazem as therapeutic agents is no longer in doubt. Nifedipine and diltiazem are efficacious in relieving angiospastic angina, and verapamil is the drug of choice for the termination of supraventricular reentrant tachycardias. In the following I will focus on the main therapeutic applications of nifedipine, diltiazem and verapamil.

Angiospastic angina: Spontaneous angina with reversible "infarct-like" electrocardiograms (marked S-T elevation and transient Q waves) was well described by the classical electrocardiographers who attributed the episodes to coronary spasm.[83] However, this pathophysiologic mechanism remained speculative until the occurrence of coronary spasm was documented by modern angiographic techniques. Japanese workers[84–86] were pioneers in studying the effects of newly developed vasodilators on coronary vasospasm. A case collection from 11 Japanese centers[87] revealed the extraordinary efficacy of nifedipine and diltiazem for the relief of coronary spasm. These agents were found to eliminate chest pain in approximately 75 percent of the patients, and improvement was noted in over 90 percent of the patients (Table II). Interestingly, verapamil was strikingly less effective than nifedipine and diltiazem. Subsequently, Yasue and collaborators[88–90] found that coronary spasm triggered by exercise or alkalosis (Tris-buffer infusion; hyperventilation)[90] could be prevented by nifedipine and diltiazem. Furthermore, they observed[89] that in some cases beta blockade with propranolol was not only ineffective in suppressing the attacks, but aggravated the disease in 8 of 13 patients. In other reports,[91,92] patients were described in whom nifedipine abolished spasm producing life-threatening ventricular arrhythmias. The efficacy of nifedipine in the treatment of angiospastic angina has widely been confirmed.[86,93]

Angina pectoris: Nifedipine appears to be less effective for the treatment of anginal syndromes not attributable to coronary spasm.[93] In six controlled studies

TABLE II

Effect of Antianginal Agents on Variant Angina (11 Japanese institutions)

	Total Cases (n)	Complete Elimination of Attacks	Decrease of Attacks to Less Than Half	No Effects	% of Effective Cases
Nifedipine	149	115	25	9	94.0
Diltiazem	87	70	9	8	90.8
Nifedipine + diltiazem	15	11	4	0	100.0
Verapamil	28	3	21	4	85.7

totaling 199 patients, nifedipine, 10 mg/8 hours orally, decreased on average the frequency of anginal attacks by 60 percent. Current evidence indicates that therapy with nifedipine plus beta receptor blockade yields better results than either nifedipine or beta receptor blockade alone.[93]

Arrhythmias: Nifedipine has no antiarrhythmic activity.[79] Verapamil, 0.15 mg/kg intravenously, is the drug of choice for the treatment of reentrant supraventricular tachycardia, irrespective of whether reentry is intranodal or occurs in association with an accessory pathway.[77,94,95] Verapamil probably acts by lengthening the effective and functional refractory period of the A-V node and prolonging the A-V nodal transmission time. Reversion to sinus rhythm occurs in a very large percent (more than 90 percent of the patients.[77,94,95] Verapamil may slow the ventricular rate in the presence of atrial fibrillation or flutter.[96] Verapamil does not appear to be a very effective drug for the treatment of ventricular arrhythmias.[96]

Of particular interest are ventricular arrhythmias during acute myocardial ischemia. It has been postulated that during ischemia potassium accumulating around the cells and other factors partly depolarize the cells, inactivating the fast channels. The cells would then depend on slow-channel action potentials ("slow response") that might be arrhythmogenic. It is further postulated that inhibition of such slow responses with a Ca^{++} antagonist should exert an antiarrhythmic effect. Ischemia impairs local conduction, and the inhibitory effects of a Ca^{++} antagonist should further accentuate impaired conduction. In dogs with experimental ischemia it has been shown that verapamil improves conduction in ischemic zones.[97–99] The reason for this paradoxical effect is not clear, but may be due to the fact that verapamil, by augmenting collateral flow, improves the electrophysiologic performance of the ischemic heart.

Arterial hypertension: There is considerable evidence that Ca^{++} antagonists may have a place in the treatment of arterial hypertension. Nifedipine has been shown to lower promptly the arterial pressure in hypertensive crises[100] and in severe essential hypertension.[101] Other investigators,[102] however, have concluded that nifedipine, 10 mg orally every 8 hours has only a modest hypotensive activity. Similarly, verapamil, 320 to 640 mg every 24 hours, has been found to produce only small decreases in arterial pressure.[103] It appears likely that Ca^{++} antagonists will be useful for the treatment of mild hypertension complicated by coronary disease or impaired left ventricular performance, or both.[64]

Left ventricular failure: Vasodilator therapy of left ventricular failure with Ca^{++} antagonists has not been extensively evaluated. In patients with coronary disease and left ventricular failure, nifedipine has been found to improve exercise tolerance and reduce pulmonary occlusion pressure.[64]

Acute myocardial infarction: In conscious dogs with coronary ligation, nifedipine administered intravenously has been shown[104] to improve collateral flow to ischemic zones, and to reduce ischemic injury assessed histologically and biochemically. In open chest dogs, nifedipine has also been shown[105] to improve regional shortening and increase local heat development in the ischemic zones. On the other hand, verapamil given to open chest dogs with coronary ligation has been reported[106] to selectively depress contractility in ischemic zones. Nevertheless, verapamil appears to reduce infarct size in dogs subjected to coronary occlusion.[107] There are no published data on the effects of Ca^{++} antagonists on myocardial infarct size in human beings.

Cardiac preservation: In isolated rabbit hearts perfused at low flow, nifedipine has been shown[108] to inhibit the development of myocardial contracture, improve recovery after reperfusion and depress the accumulation of Ca^{++} in the mitochondrial fraction of ventricular myocardium. Similarly, verapamil has been noted[109] to inhibit hypoxic contracture in the isolated perfused guinea pig heart. In dogs undergoing total hypothermic cardiopulmonary bypass for 2 hours, nifedipine has been shown[110] to exert striking protective effects on the heart.

Cardiomyopathy: Jasmin et al.[111] demonstrated that verapamil prevents the development or reduces the severity of heart lesions in the cardiomyopathic hamster. Of considerable interest are reports[112,113] indicating that long-term treatment with verapamil may beneficially influence hypertrophic obstructive cardiomyopathy in man.

In conclusion: Ca^{++} antagonists are a rather heterogeneous class of agents with dissimilar structural, electrophysiologic and pharmacologic properties. There are still some questions regarding the clinical utility of the concept of Ca^{++} antagonism. However, the evidence is overwhelming that some of these agents are of great value for the treatment of specific cardiovascular disease states.

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Effects of Nifedipine on Electrical Activity of Cardiac Cells

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The effects of nifedipine were studied on action potentials recorded from (1) normal canine Purkinje fibers, (2) Purkinje fibers exposed to barium chloride (0.1 to 0.25 m*M*), which reduces their membrane potential and produces enhanced pacemaker activity (abnormal automaticity), and (3) subendocardial Purkinje fibers underlying infarct zones at 24 hours after ligation of the left anterior descending coronary artery. In concentrations of 0.1 to 0.3 mg/liter, nifedipine did not significantly alter the resting transmembrane potential, action potential amplitude or maximal upstroke velocity of normal Purkinje fibers. The action potential duration (to 50 and 100 percent repolarization) was significantly shortened. These concentrations of nifedipine did not suppress the slope of phase 4 depolarization of automaticity in Purkinje fibers with maximal diastolic potentials between −85 and −95 mV.

Abnormal automaticity in fibers exposed to barium chloride (Ba^{++}), having maximal diastolic potentials of −40 and −60 mV, was promptly abolished by nifedipine in concentrations of 20 to 200 μg/liter (n = 12). In slightly higher concentrations (0.2 to 0.6 mg/liter), nifedipine slowed or stopped abnormal automaticity in infarct zone Purkinje fibers (n = 3). In two subendocardial Purkinje fiber preparations, salvos of spontaneous impulses were observed that were terminated with delayed afterdepolarizations; nifedipine (0.1 to 0.2 mg/liter) quickly abolished these impulses.

It is concluded that nifedipine can suppress abnormal automatic activity in canine cardiac Purkinje fibers in concentrations of 20 to 200 μg/liter, concentrations that will only shorten the plateau of normal action potentials. Nifedipine may prove to be a useful antiarrhythmic drug.

Patients with coronary artery disease or Prinzmetal's angina have increased risks of life-threatening ventricular arrhythmias.[1–4] The commonly prescribed antiarrhythmic drugs have not been proved to decrease the incidence of sudden death in these patients.[5] There is some evidence that beta adrenergic blocking drugs, which frequently are used to treat angina pectoris, prevent arrhythmias[6] and may provide some protection against sudden death.[7,8] The fact that a single drug might relieve ischemia and at the same time decrease the likelihood of fatal ventricular arrhythmias suggests that other types of antianginal agents should be tested for antiarrhythmic efficacy.

Nifedipine is one such agent that has been reported to be extremely effective for alleviating both stable and variant angina.[9–12] Nifedipine is thought to relax vascular smooth muscle by blocking transmembrane calcium fluxes.[13,14] There is evidence that it exerts similar effects on myocardial fibers by shifting the plateau of ventricular muscle to less positive voltages, decreasing action potential duration and exerting a strong negative inotropic effect,[12,15,16] and blocking the "slow inward current" in experiments with the voltage clamp.[17]

Inhibitors of the slow inward current in cardiac cells might be able to abolish arrhythmias generated by several mechanisms, including reentry,

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abnormal automaticity and triggered responses. Reentry in ischemic cardiac tissue presumably depends on unidirectional block and slow conduction[18]; one mechanism for very slow propagation of the cardiac impulse is the replacement of the normal fast response by the slow response.[19] The slow response depends on an inward depolarizing current in the "slow" channels (g_{si}) that is carried primarily by calcium ions, and can be elicited in partially depolarized fibers. Another mechanism for the production of arrhythmias is "abnormal automaticity" (that is, enhanced impulse initiation in partially depolarized cells). Abnormal automaticity can occur in depolarized working myocardial cells or in cells of the conduction system. If the membrane potential is sufficiently reduced, the automatic impulses are predominantly slow responses and result largely from an inward calcium current.[20,21] The third mechanism for abnormal impulse generation is the triggered response,[19,22] which can result from either early or delayed afterdepolarizations. In the case of early afterdepolarizations, the repetitive responses once again can be classified as slow responses, because they arise at membrane potentials so close to zero that the fast inward (sodium) channels are likely to be very largely inactivated. In fibers that are not excessively depolarized, the current responsible for delayed afterdepolarizations is now thought to be a sodium current.[23] Nevertheless, some delayed afterdepolarizations also depend on a transmembrane calcium current,[24,25] which causes an excessive increase in intracellular calcium activity. This, in turn, is thought to initiate an oscillatory release and reuptake of calcium ion from intracellular stores. The oscillatory changes in intracellular calcium activity are a possible cause of the changes in membrane ionic conductance that result in a transient inward current and delayed afterdepolarizations. A more detailed description of these mechanisms is provided elsewhere.[26]

We thought it important to study the effects of nifedipine on several cell mechanisms of arrhythmias. Our primary objective was to evaluate its actions on abnormal automaticity and delayed afterdepolarizations. At the same time, we thought it necessary to study in some detail its effects on the electrical activity of normal Purkinje fibers to see whether it exerted effects like those of standard antiarrhythmic drugs to depress conduction and normal automaticity.

Methods

Studies on isolated canine Purkinje fibers: Mongrel dogs were anesthetized with pentobarbital (30 mg/kg body weight, intravenously) and the heart was excised rapidly and immersed in a large volume of cold Tyrode's solution. False tendons (that is, bundles of Purkinje fibers) were excised from both the right and left ventricles. One bundle was placed in a tissue bath that has previously been described.[27] The fiber was superfused with Tyrode's solution at a rate of 10 to 12 ml/min. The Tyrode's solution had been equilibrated with a mixture of 95 percent oxygen and 5 percent carbon dioxide and warmed to 37° C before entering the tissue bath. The volume of the tissue bath was less than 10 ml.

The preparations were stimulated with rectangular pulses through a pair of Teflon®-coated silver wire electrodes positioned at one end of the false tendon. Transmembrane potentials were recorded through glass capillary microelectrodes filled with 3*M* of potassium chloride (KCl) and having direct current resistance of 10 to 25 megohms. The intracellular microelectrodes were coupled through silver-silver chloride interfaces to amplifiers with high input impedance and the capability for capacity neutralization. The tissue bath was connected to ground through a similar 3*M* of KCl silver-silver chloride sequence. A calibrator between the bath electrode and ground provided calibration for records of membrane potential and the first time derivative of membrane potential.[28] For most experiments, two microelectrodes were used to record transmembrane potentials simultaneously from two fibers at different locations in the preparation. Data were deemed acceptable if the impalement in each fiber was maintained for the duration of the test procedure.

For studies on normal Purkinje fibers, the preparation was stimulated at selected cycle lengths to demonstrate effects on transmembrane potentials and on the slope of phase 4 depolarization of a driven preparation. For experiments on normal automaticity, the drive stimulus was interrupted periodically to assess the intrinsic rhythmicity of the false tendon. For these experiments the potassium concentration in the Tyrode's solution was 2.7 m*M*. For all other experiments, potassium was 4 m*M*. The composition of the Tyrode's solution in m*M* was: sodium chloride (NaCl), 137; sodium bicarbonate ($NaHCO_3$), 12.0; calcium chloride ($CaCl_2$), 2.7; magnesium chloride ($MgCl_2$), 0.5; sodium phosphate (NaH_2PO_4), 1.8; glucose, 5.5. The pH was 7.35 to 7.42.

The experiments were conducted in the dark with the room illuminated by darkroom lights to avoid photolytic degradation of nifedipine. The drug was added to the stock Tyrode's solution to produce final concentrations ranging from 20 to 300 mg/ml. Records were obtained under control conditions, during superfusion with Tyrode's solution containing graded concentrations of nifedipine and then during a washout with drug-free solution.

Studies on fibers exposed to barium chloride: It has been shown that barium chloride, in concentrations of 0.75 to 5.0 m*M*, probably by decreasing the conductance of the membrane to potassium, causes partial depolarization of ventricular muscle and the appearance of abnormal automaticity.[29–31] This is characterized by a maximal diastolic potential in the range of −60 to −40 mV, typical phase 4 depolarization and action potentials with a slow upstroke and small overshoot. We used barium chloride in concentrations between 0.1 and 0.25 m*M* to induce normal automaticity in Purkinje fibers. Once stable abnormal automaticity was obtained, nifedipine was used in concentrations between 20 and 300 μg/liter. In some experiments, driving stimuli were used periodically to test whether or not an intrinsic rhythm could be reinduced after exposure to nifedipine.

Studies on subendocardium from 24 hour infarcts: In another group of experiments we studied the effects of nifedipine on subendocardial tissues excised from dog hearts with a 24 hour infarct. On the day before the experiment, the left anterior descending coronary artery was ligated in two stages according to the method of Harris.[32] The chest was then closed and the animal allowed to recover. Approximately 24 hours after coronary ligation, when ventricular arrhythmias were most prominent, the dog was anesthetized with pentobarbital and the heart excised and cooled in Tyrode's solution. The left ventricle was opened and two to four preparations of endocardial tissue, each about 10 by 15 mm in surface area and

1 mm thick, were excised from the infarct zone and one placed in the tissue bath. Stimulation and recording techniques were similar to those described for isolated false tendons. These preparations were used to study abnormal automaticity and delayed afterdepolarizations. Records were obtained either by photographing a Tektronix 565 oscilloscope with a Polaroid® camera or from a Gould-Brush recorder (model 2400). The latter could not be used to record faithfully the action potential amplitude of normal Purkinje fibers because of its limited frequency response, but was suitable to obtain continuous records of slower transients.

Results

Normal cardiac Purkinje fibers: Each Purkinje fiber preparation was driven at a cycle length of 1000 ms and allowed to equilibrate for 60 minutes to obtain stable control records. The fibers showed normal values for resting transmembrane potential (−94 ± 1.4 mV), action potential amplitude (126 ± 4.5 mV) and maximal rate of depolarization during phase 0 of the transmembrane action potential ($\dot{V}_{max}$, 485 ± 60 V/s). Typical control records are shown in the upper panel of Figure 1. Nifedipine was then added to the superfusate in a concentration of 100 μg/liter. The records were monitored for 30 to 40 minutes, the values at this time were recorded and then the concentration of nifedipine was increased to 300 μg/liter. Again, the observation period was 30 to 40 minutes. Finally, the preparation was superfused with drug-free Tyrode's solution to permit a search for reversal of effects.

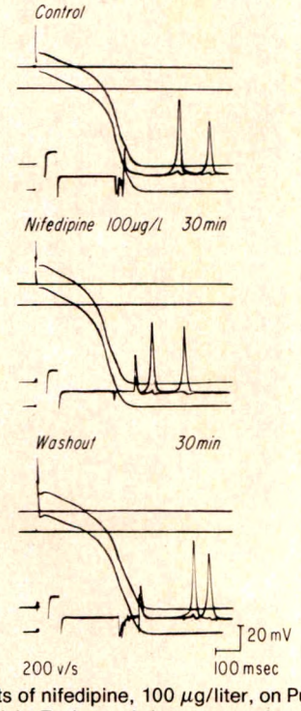


FIGURE 1. Effects of nifedipine, 100 μg/liter, on Purkinje fiber transmembrane potentials. Each panel shows two action potentials recorded from sites about 2 mm apart. Zero potential reference lines and differentiated upstrokes of phase 0 ($\dot{V}_{max}$) are shown for each action potential. $\dot{V}$ calibration = 200 V/s. Voltage and time calibrations are shown at **lower right.**

Nifedipine had little effect on normal transmembrane potentials in either concentration (Fig. 1, Table I). There was no change in resting transmembrane potential or action potential amplitude and no decrease in $\dot{V}_{max}$. At a concentration of 100 μg/liter nifedipine did cause some change in the plateau and action potential duration. There was no shift in the voltage level of the plateau but its duration decreased, and action potential duration at 50 percent repolarization (APD 50 percent) and at full repolarization (APD 100 percent) was significantly shortened (Table I). There were no changes in the voltage-time course of phase 3. Exposure to nifedipine in a concentration of 300 μg/liter caused no additional decrease in either APD 50 percent or APD 100 percent and no change in the other variables. Washout of nifedipine was followed for 30 to 120 minutes. Action potential duration returned to control values within 60 to 90 minutes.

In five experiments we studied the effects of nifedipine on normal phase 4 depolarization of Purkinje fibers driven at a cycle length of 4,000 ms. Nifedipine in concentrations of 100 and 300 μg/liter did not decrease the slope of phase 4 depolarization (Fig. 2). Also, these concentrations did not suppress automatic impulse generation in normal spontaneously firing Purkinje fibers with normal maximal diastolic potentials of −85 to −95 mV. In a few instances there was a suggestion that nifedipine slightly increased normal automaticity (Fig. 2).

Effects of nifedipine on abnormal automaticity induced in isolated Purkinje fibers by exposure to low concentrations of barium chloride: Abnormal automaticity was induced in nine preparations of normal Purkinje fibers in isolated false tendons by superfusing them with Tyrode's solution containing barium chloride ($BaCl_2$) in concentrations of 0.10 to 0.25 m*M*. The false tendons were driven at cycle lengths of 2,000 to 4,000 ms as the barium was introduced, and when spontaneous activity began the stimulus was turned off. Exposure to barium caused rapid changes in the transmembrane potentials. There was a prompt de-

TABLE I

Cardiac Purkinje Fiber Transmembrane Potentials

	RMP	APA	$\dot{V}$max	APD 100%	APD 50%
Control	−94 ±1.4 mV	126 ±4.5 mV	485 ±60 V/s	450 ±10 ms	298 ±15 ms
Nifedipine 100 μg/liter	−92 ±1.1	126 ±4.9	519 ±64	428* ±3	264* ±8
Nifedipine 300 μg/liter	−92 ±1.1	127 ±5.3	545 ±70	431* ±5	254* ±12

* Probability (p) = 0.05 versus control values. The values shown represent mean ± standard deviation for cells driven at a cycle length of 1,000 ms. n = 8.

APA = action potential amplitude; APD = action potential at 100 and 50 percent repolarization, respectively; RMP = resting transmembrane potential; Vmax = maximal rate of depolarization.

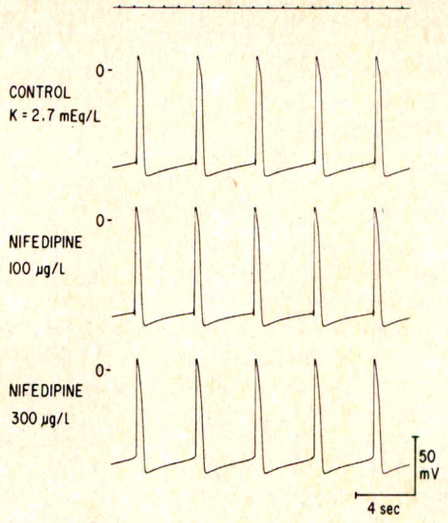


FIGURE 2. Effects of nifedipine on the slope of normal phase 4 depolarization. Time and voltage calibrations, **lower right;** zero reference potential, **left of each panel. Top panel,** control records from a fiber driven at a cycle length of 4,000 ms. **Middle and lower panels,** transmembrane potentials after 30 minutes exposure to nifedipine, 100 and 300 µg/liter, respectively. **Lower panel,** preparation just before it became automatic at a cycle length of about 3,600 ms. Action potential amplitudes and overshoots are attenuated in this and all subsequent figures because recordings were taken on a pen recorder (Gould 2400).

crease in maximal diastolic potential from the control value to values between −62 and −40mV. This change required 3 to 5 minutes. Concomitantly there was a decrease in action potential amplitude and overshoot, a marked slowing of the action potential upstroke and the appearance of fairly marked phase 4 depolarization. Under control conditions the cells in the barium-treated preparations generated automatic impulses at a steady rate for periods of several hours. The action potentials generated under these conditions appear to be slow responses (unpublished observations) and are abolished by other agents like verapamil or AHR-2666,[33,34] which are thought to block the slow channels (g_{si}) and diminish slow inward current.[35,36]

In the nine preparations, the Purkinje fibers fired at a cycle length of 860 ± 220 ms (mean ± standard deviation). After a 30 to 60 minute observation period had elapsed, to be sure that the abnormal automaticity was stable, the superfusate was changed to one that contained nifedipine in concentrations of 20 to 200 µg/liter. In every experiment, the abnormal automatic activity was promptly arrested after exposure to nifedipine. In each experiment, the total amplitude of the action potentials decreased before abolition of automaticity. This decrease in amplitude represented a reduction of both the overshoot and the maximal diastolic potential. In five of the impalements, the amplitude of the action potentials was markedly reduced (to less than 50 per-

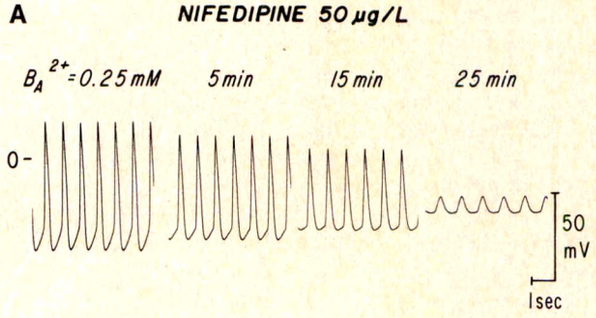
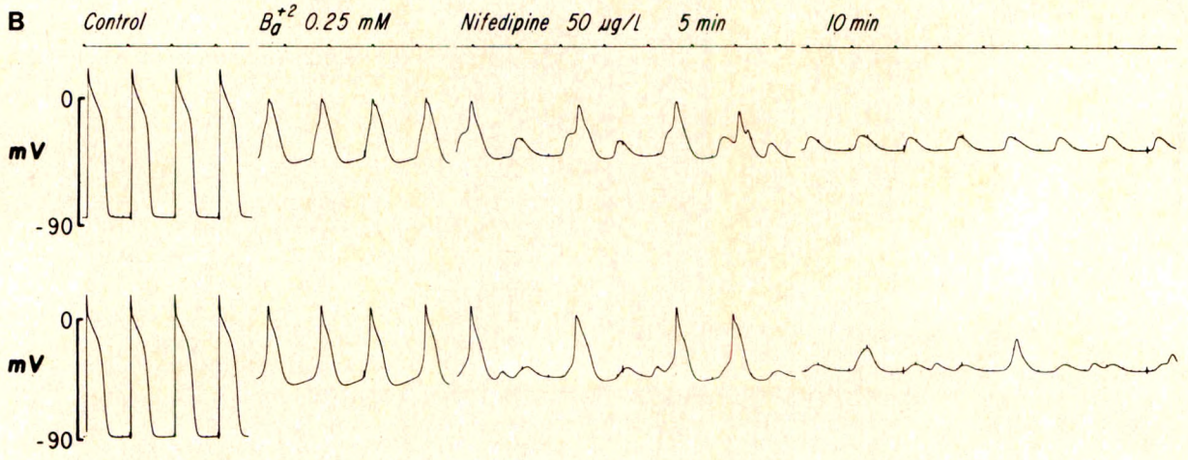


FIGURE 3. Effects of nifedipine, 50 µg/liter, on abnormal automaticity induced by barium (Ba^{2+}). **A, From left to right,** panels show control recordings, and records taken 5, 15 and 25 minutes after start of exposure to nifedipine. At 25 minutes, action potential amplitude was markedly reduced, and within 30 minutes all activity arrested. Similar effects occurred at a second site approximately 7 mm away. Time and voltage calibrations and zero reference potentials as in Figure 2. **B, From left to right,** panels show control recordings at two sites, effects of barium chloride, and effects of nifedipine, 50 µg/liter, at 5 and 10 minutes. By 5 minutes, most impulses did not produce full regenerative responses at either site, and by 14 minutes all activity had arrested (not shown).



cent of the control amplitude) for several minutes before all activity ceased (Fig. 3) whereas in 11 Purkinje cells there were small (5 to 20 percent) decreases in amplitude before arrest. In 7 of these 11 fibers, subthreshold oscillations resembling delayed afterdepolarizations followed the final regenerative response (Fig. 4), whereas no afterpotentials were observed in the remaining four impalements.

Abolition of abnormal automaticity was not the only action exerted by nifedipine on the barium-treated fibers. With longer exposure, nifedipine increased the threshold for electrical stimulation and blocked regenerative responses.

A representative example is shown in Figure 5. Sixty seconds after nifedipine had arrested abnormal automaticity in a barium-treated fiber, a 16 second train of stimuli (500 ms cycle length) elicited a series of 35 triggered potentials. Three minutes later, the same stimulus train produced no triggered responses, and the stimulated action potentials were markedly reduced in amplitude. Two minutes later, the preparation was inexcitable (not shown).

In one experiment, a 10 by 15 mm slice of subendocardial tissue was superfused with Tyrode's solution containing $BaCl_2$, 2.0 m*M*. Transmembrane potentials recorded from subendocardial Purkinje fibers in this preparation were reduced to −55 to −60 mV and showed repeated bursts of 30 to 50 action potentials that lasted 60 to 90 seconds. The bursts were separated by quiescent periods of 35 to 60 seconds, and each burst terminated with a delayed afterdepolarization. Activity persisted in the presence of a low concentration of nifedipine (50 μg/liter) in the superfusate, but when the concentration was increased to 100 μ/liter, the duration of the bursts gradually shortened and the delayed afterdepolarizations disappeared. After 25 minutes no bursts occurred, and by 27 minutes all spontaneous impulse initiation had been abolished.

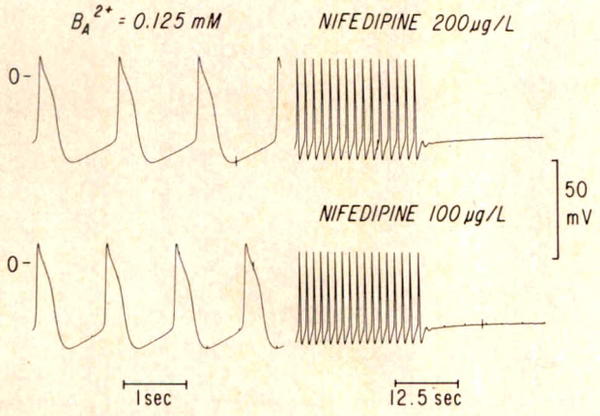


FIGURE 4. Subthreshold oscillations after exposure to nifedipine. **Upper left,** records for fiber in Tyrode's solution containing Ba^{2+}; **upper right,** arrest of activity by nifedipine, 200 μg/liter. The drug was washed out for 120 minutes, and the sequence repeated with 100 μg/liter (**lower panels**). Spontaneous activity was restored after first period of exposure to nifedipine using extracellular stimulation. Zero potentials, at **left,** voltage calibration, at **right,** and time calibration for **right and left panels** appears below them.

Effects of nifedipine on abnormal impulse initiation in subendocardial Purkinje fibers in 24 hour infarct zones: The effects of nifedipine on abnormal impulse initiation in 24 hour infarct zones were studied in four preparations. In three experiments, one or more impalements in the surviving subendocardial Purkinje fiber network showed abnormal automaticity. In the fourth experiment, triggered activity with delayed afterdepolarizations was recorded.

Abnormal automaticity in sections of infarcted tissue is more variable and less stable than that which can be induced with barium. The maximal diastolic potentials can vary greatly over the surface of the infarct slice. In only one of the three experiments on infarct zone abnormal automaticity, all spontaneous activity was promptly terminated after exposure to nifedipine (Fig. 6). In this experiment the action potential amplitude was markedly reduced within 5 minutes after exposure to nifedipine, 200 μg/liter, a result similar to that often obtained in studies on the barium-treated fibers. In each of the other two experiments in infarct zone abnormal automaticity, the rate of impulse initiation was greatly slowed in 15 to 30 minutes, but not stopped (Fig. 7). The spontaneous cycle lengths increased from 575 to 1,190 ms in one experiment and from 1,400 to 2,250 ms in the other.

Not all preparations of 24 hour infarct zone endocardium showed Purkinje fibers with abnormal automaticity and low (−40 to −60 mV) maximal diastolic potentials. In several preparations, cells with more

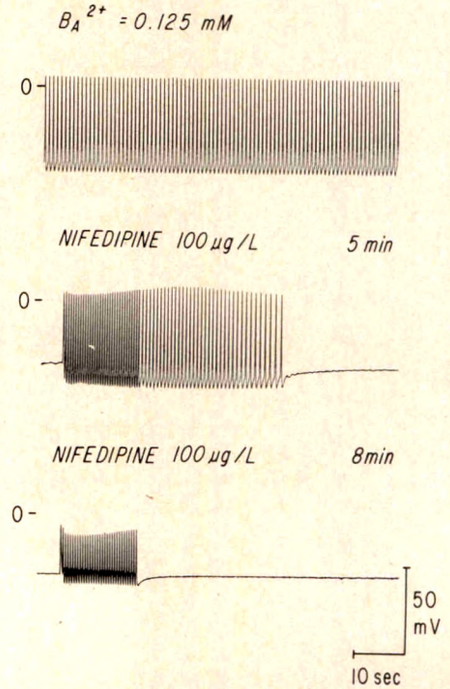


FIGURE 5. Effects of nifedipine on triggered responses in Purkinje fibers depolarized with barium chloride. Format as in Figure 2. For detailed explanation see text.

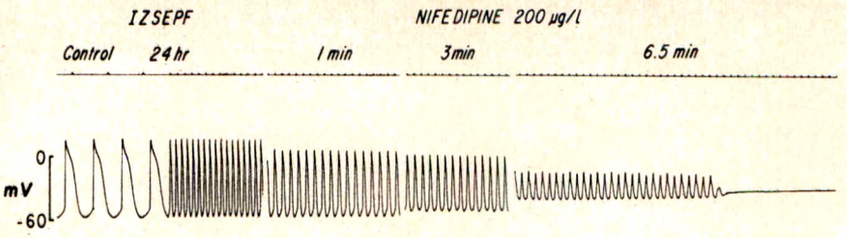


FIGURE 6. Reduction of action potential amplitude and abolition of spontaneous activity in infarct zone subendocardial Purkinje fiber (IZSEPF) exposed to nifedipine. **First panel from left,** control recordings taken at fast and slow paper speeds. **Second, third and fourth panels,** development of effects of nifedipine, 200 µg/liter. Records taken at times indicated after start of drug perfusion. Voltage calibrations shown at **left,** 1 second time marks, **above.**

normal maximal diastolic potentials (−75 to 90 mV) were studied. When these cells were driven with trains of 5 to 20 stimuli at cycle lengths of 800 to 1,200 ms, three of them showed triggered extra responses or delayed afterdepolarizations, or both. When spontaneous activation was allowed, one of these preparations remained quiescent, while the other two fired bursts of action potentials like those previously described for the $BaCl_2$-treated subendocardial fibers. Each burst lasted 60 to 90 seconds, but would continue for longer periods if epinephrine was added to the superfusate. Typically, the pattern of action potential bursts was very stable. Within each burst, the rate of firing was slow at first and then accelerated to a minimal cycle length of about 800 ms. The maximal diastolic potential gradually increased during the burst, as seen during "overdrive hyperpolarization." Finally, the rate of impulse initiation slowed and the burst was terminated with a subthreshold oscillation.

One experiment was performed to test the effects of nifedipine on this type of activity (Fig. 8). Within 8 minutes of exposure to nifedipine, 200 µg/liter, the triggered bursts of action potentials were abolished. Washout of the drug for 90 minutes resulted in restoration of the bursts of action potentials.

Discussion

Effects of nifedipine on normal Purkinje fibers: Drugs such as verapamil and D-600[35] and AHR-2666,[36] that have as their primary effect blockade of the slow inward channel in cardiac fibers, cause rather prominent changes in the configuration of transmembrane potentials of the cardiac Purkinje fibers. Probably as a result of block of slow inward current, they shift the plateau to more negative voltages and decrease the duration of the action potential in the range of plateau voltages. In addition, however, they cause some decrease in the slope of phase 3 and a resulting increase in overall action potential duration. This effect may result from an action on a potassium channel ($i_{x,1}$) thought to be

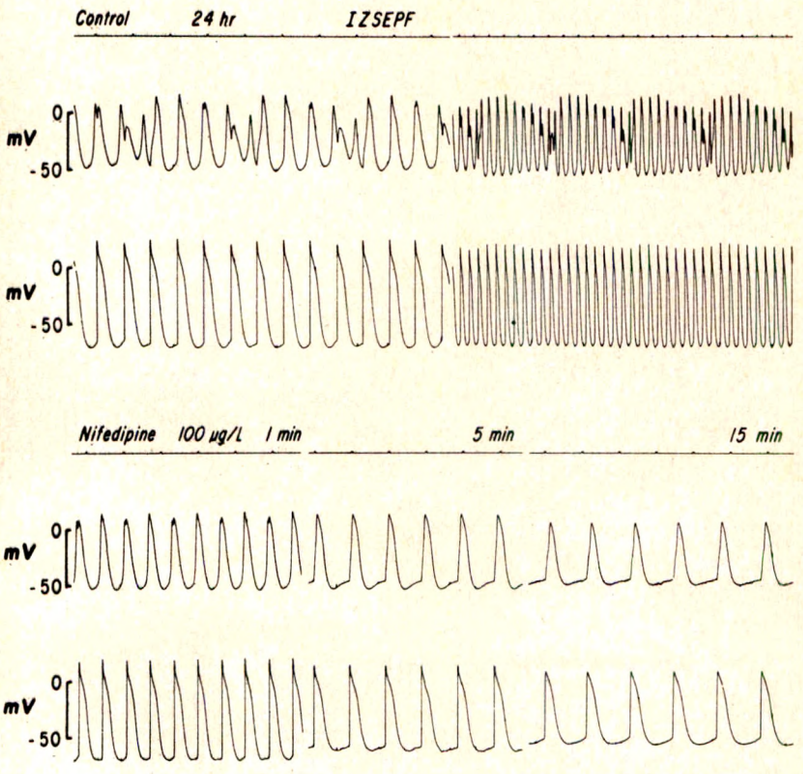


FIGURE 7. Slowing of automaticity in a preparation of 24 hour infarct zone Purkinje fibers (IZSEPF). Each panel shows recordings from two different cells about 5 mm apart. **Upper panels,** control recordings: standard paper speed at **right,** slow speed at **left** to illustrate periodicity of activity in recording at **top. Lower three panels,** effects of nifedipine, 100 µg/liter. By 1 minute after start of exposure to the drug, the highly aberrant activity in the recording at the top of the panels was abolished, and by 15 minutes the preparation was activated at a cycle length of 1,190 ms. Exposure to nifedipine, 300 µg/liter, for 30 minutes did not produce further slowing.

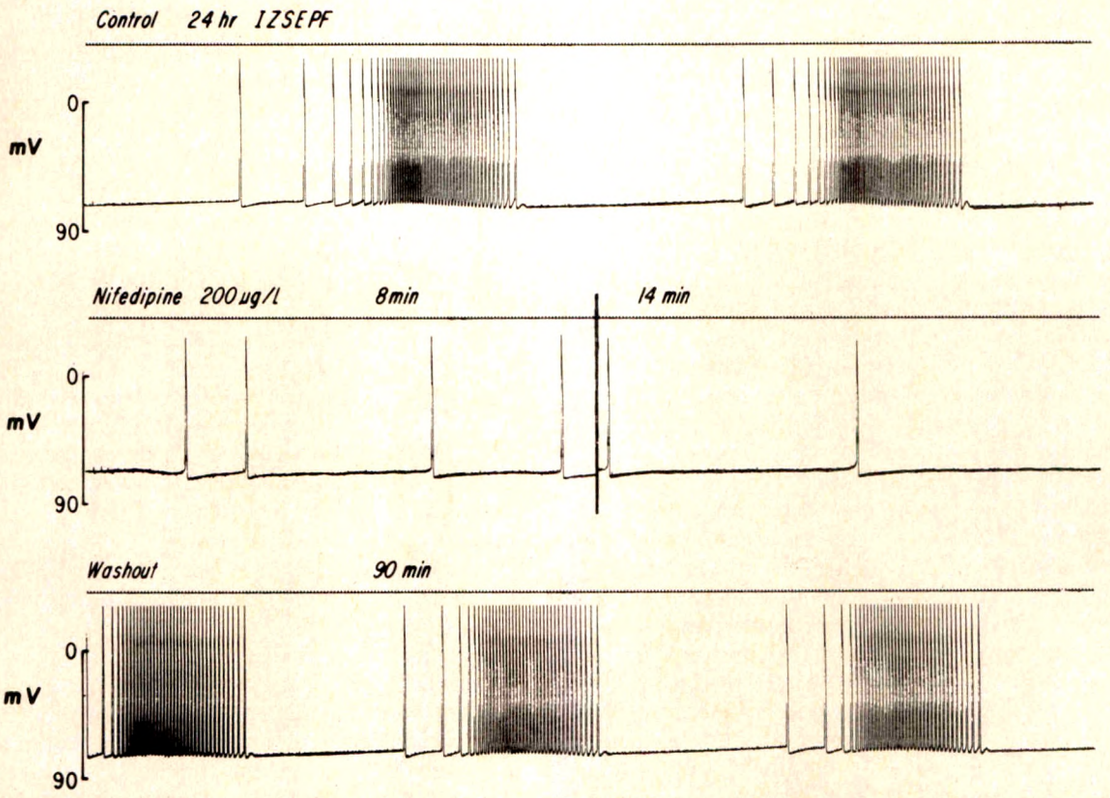


FIGURE 8. Effects of nifedipine on bursts of action potentials occurring in preparation of a subendocardial Purkinje fiber of a 24 hour infarct zone (IZSEPF). **Upper panel,** control recordings; **middle panel,** the effects of the drug; **lower panel,** washout of the drug. Within 8 minutes after start of nifedipine, 200 µg/liter, bursts of action potentials were abolished, and final spontaneous action potentials were recorded at 14 minutes. No subsequent spontaneous action potentials occurred for an additional 16 minutes while drug superfusion continued. Note voltage calibrations at **left,** 1 second time marks **above each** panel. For further discussion, see text.

responsible for repolarization or may reflect the effect of a change in intracellular calcium activity on potassium (K^+) conductance.[37] Verapamil decreases the slope of phase 4 depolarization and the maximal rate of rise of the action potential upstroke in a manner resembling the effects of the local anesthetic antiarrhythmic drugs.[38,39]

Our findings for nifedipine resemble in general those published by other investigators[13,16] for ventricular muscle fibers. In concentrations up to 300 µg/liter, nifedipine acts mainly to modify the plateau phase of the Purkinje fiber transmembrane action potential. We found no significant effect on the resting potential, action potential amplitude or the maximal rate of depolarization during phase 0. One thus would expect in the intact heart no decrease in the speed of impulse conduction in the specialized ventricular conducting system and no major change in its refractoriness. Nifedipine did not decrease the slope of phase 4 depolarization in normal Purkinje fibers and over the range of concentrations studied would thus not be expected to depress the intrinsic automaticity of specialized ventricular fibers. The slight increase in automaticity noted in some experiments may be related to local release of catecholamines.

Thus, in a heart in which the fibers of the specialized conducting system are normal, one would not expect nifedipine to slow conduction, increase the duration of the QRS complex or cause focal conduction block. Also, in the presence of atrioventricular block, nifedipine would not impair the ability of latent pacemakers in the ventricular conducting system to generate a spontaneous rhythm. This is a significant problem of a number of the standard antiarrhythmic drugs.

Effects on abnormal automaticity in fibers exposed to barium: The model used for these studies probably deserves some comment. A major effect of low concentrations of barium on cardiac fibers is to decrease the conductance of the membrane to outward potassium currents. It is very likely that a decrease in outward background current ($gK_{,1}$) is responsible for the reduction in maximal diastolic potential from the normal value of greater than −90 mV to a value less negative than −65 mV. When maximal diastolic potential is between −40 to −60 mV, Purkinje fibers typically show depolarization during phase 4, which results in automatic impulse generation. The transmembrane action potentials initiated by this mechanism show a low rate of depolarization during phase 0 and frequently resemble transmembrane action potentials generated by fibers in the sinoatrial node. The slow depolarization during phase 4 may be caused by a time- and voltage-

dependent decrease in the repolarizing potassium current, $i_{x,1}$. The slowly rising action potentials result in large part from inward current carried by calcium ions in the slow inward channels.[20]

Modification of automatic impulse generation in this preparation might be brought about by an agent that reduced the slope of phase 4 depolarization, shifted the threshold potential toward 0 or decreased the ability of the fiber to generate a slow inward current sufficiently large to generate an action potential. Nifedipine usually did not have prominent effects on the slope of phase 4 depolarization; however, it was effective in abolishing automatic impulse generation. In some instances the automatic rhythm terminated rather abruptly as a result of failure of the phase 4 depolarization to attain threshold, with the final action potential being followed by "delayed afterdepolarization." In other cases, nifedipine caused a progressive decrease in the amplitude of the action potential until only small subthreshold depolarizations were recorded. Both of these effects can be attributed to blockade of slow inward current. In each instance, after nifedipine had abolished automatic impulse generation, the addition of epinephrine or norepinephrine to the superfusate restored phase 4 depolarization and spontaneous activity resembling that seen before exposure to nifedipine (data not shown). Catecholamines are known to augment slow inward current in cardiac fibers,[40] and this finding is compatible with the interpretation that the effect of nifedipine resulted from a reduction in slow inward current. Because nifedipine did not have prominent effects on the slope of phase 4 depolarization one can assume that it does not have important effect on the $i_{x,1}$ channel. This finding is supported by the data for normal Purkinje fibers because nifedipine did not significantly alter the voltage-time course of membrane potential during the latter part of phase 3.

The generation of impulses by the Purkinje fibers exposed to low concentrations of barium appears to be automatic. At the same time, fibers in this condition also may generate delayed afterdepolarizations and triggered rhythms.[22] Indeed, in many instances when nifedipine terminated spontaneous impulse generation, the record of transmembrane potential showed one or more oscillatory depolarizations of low amplitude that can be classified as delayed afterdepolarizations (Fig. 4). Also, the pattern of the change in rhythm of some partially depolarized preparations from infarcted hearts suggested the presence of an underlying automatic rhythm that periodically initiated a more rapid triggered rhythm (Fig. 8). In both the barium-treated Purkinje fibers and the preparations from infarcts, nifedipine prevented triggering.

Effects on subendocardial tissues from infarcted hearts: The preparations of Purkinje fibers from 24 hour infarct zones demonstrated several types of spontaneous impulse generation, as have previously been described.[41–44] The extent to which spontaneous impulse generation is the cause of the ventricular arrhythmias that typify the in situ heart at 24 hours after coronary ligation has not been precisely evaluated. Nevertheless, it seems likely that much of the ventricular ectopic activity during this period is the result of spontaneous impulse generation. In some instances, the predominant mechanism may be a form of abnormal automaticity and in others the ectopic impulses may be triggered.[26]

Our findings for nifedipine suggest that it should have no major undesirable effects on electrical activity of normal cardiac Purkinje fibers but should exert a protective effect against arrythmias caused by several of the mechanisms engendered by ischemia, if sufficiently high tissue concentrations of the drug are achieved.

Acknowledgment

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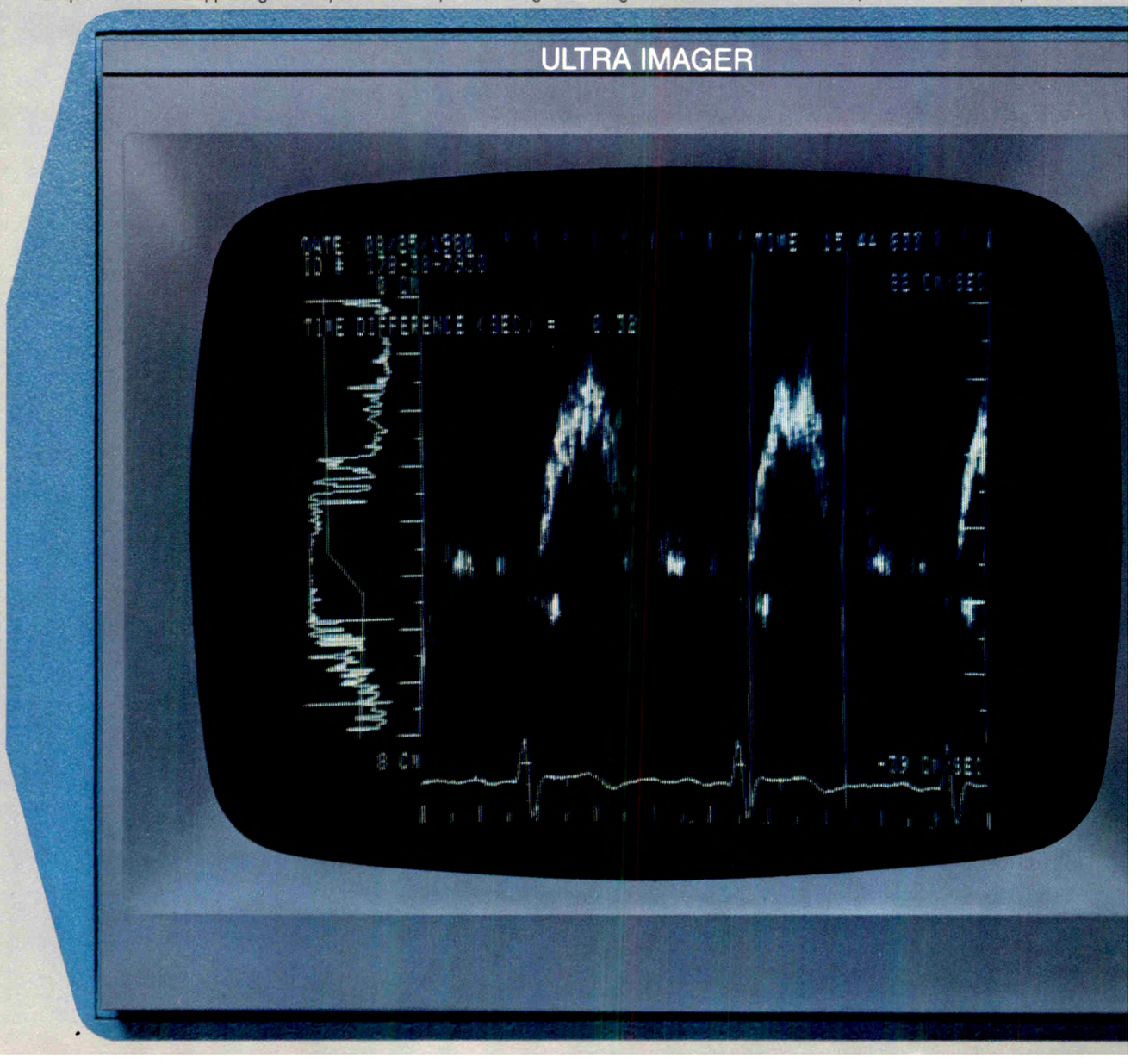
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External Pressure Circulatory Assistance: No Light on the Shadow*

LESLIE A. KUHN, MD, FACC

New York, New York

The eminent T.S. Eliot wrote: ". . . between the idea and the reality; between the motion and the act: falls the shadow." The unhappy reality and the heretofore impenetrable shadow for cardiologists treating acute myocardial infarction has been pump failure manifested by shock and advanced left ventricular failure. For this reason, attention is commanded by any study suggesting that a procedure can reduce mortality in acute myocardial infarction either by more effectively treating severe left ventricular failure and shock (the principal causes of mortality) or, preferably, by preventing their development. The cooperative study on clinical assessment of external pressure circulatory assistance published in this Journal[1] is one such study. It claims that this mechanical technique reduces mortality and morbidity in subsets of patients with acute myocardial infarction. Its publication was accompanied by an aggressive advertising campaign to the profession, and was preceded by vigorous efforts to obtain national exposure on the major television networks. Use of this apparently trendy technique—in which putative medical advances are announced to the public before they can be considered carefully by the physicians who are to judge and apply them—should, of course, be accompanied by the responsibility of having a study that is relatively flawless and that reports a truly significant advance.

After several years of the use of intraaortic balloon counterpulsation to treat patients with acute myocardial infarction and shock, the mortality rate of patients with the shock syndrome remains very high, although different studies indicate some variation in efficacy of the technique,[2–7] probably owing to different criteria in patient selection. In addition, the intraaortic balloon technique had been associated with appreciable morbidity,[3,8] although it may still be needed in light of the high risk of death in patients with cardiogenic shock. Because of the continuing very high mortality rate of patients with acute myocardial infarction once the shock state has developed despite all present modes of therapy, it is reasonable to seek to reduce mortality by treating patients with lesser degrees of circulatory and pump failure after acute infarction in an attempt to prevent the shock syndrome. If this can be accomplished by a noninvasive method that is simpler to apply and results in fewer complications than occur with the intraaortic balloon, a significant advance will have been achieved.

External Pressure Circulatory Assistance

External pressure circulatory assistance has been investigated for several years[9–12] and by now is somewhat too well known to elicit fresh excitement among cardiologists. It can produce effective diastolic augmentation of the arterial pressure, can possibly alter (as reported in some studies) myocardial metabolic abnormalities, and can possibly increase coronary blood flow. It has been shown to be less effective than intraaortic balloon pumping in "unloading" the left ventricle, as judged from the persistence of high left ventricular diastolic pressure, and some studies have reported persistence of myocardial excess lactate production. A recent study[13] of 23 patients with transmural and nontransmural myocardial infarction indicated improvement in regional wall motion abnormalities in 69 percent of patients (as judged from echocardiographic criteria) but no data were presented on alterations of wall motion abnormalities in patients not receiving external counterpulsation and there was no lessening of postinfarction angina. Pulmonary edema developed in one patient 15 minutes after the onset of treatment (could this have been due to increased venous return?). Three patients died with cardiogenic shock.

It is reasonable to investigate carefully the use of this technique in acute myocardial infarction. However, the

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* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal of the American College of Cardiology.

reported cooperative study appears to have major flaws that may substantially vitiate its conclusions.

Potential Limitations of Cooperative Study

The authors studied a total of 258 patients in 25 institutions and attempted to randomize the selection of treated (142 patients) versus control (116 patients) groups of subjects with acute myocardial infarction judged to be in Killip class II. A significant reduction in mortality is claimed for patients less than 46 years of age receiving external circulatory support for at least 3 hours in the first 24 hours of hospitalization and for the entire group receiving external support for at least 4 hours in the first 24 hours of hospitalization when compared with patients not so treated. A major effort was taken to randomize the patients to each of the two groups. However, the number of patients studied in each institution varied considerably, ranging from 1 patient (two institutions) to 26 patients (one institution) with a mean of 9 patients per institution. The small number of patients in many of the cooperating institutions would make a true randomization of patients difficult and the results very preliminary at best. How were the single patients in two institutions and the very small number of patients in other institutions randomized? It is difficult to group the patients within the study as a whole, crossing institutional lines, because standards of treatment, expertise and interpretation of results may vary considerably among institutions. The type of institution ranged from a small community hospital to a large, sophisticated medical center. Even the average number of patients (nine) studied in a single institution (about four each in control and treated groups) is probably not sufficiently large to form valid conclusions.

Although the study was apparently randomized, there was no restriction on any other form of therapy used—a factor that might well influence results—and no data were available for comparative analyses of such therapy after the 5th day. The group receiving external circulatory support had about twice as many patients with intramural infarction as did the untreated group and had fewer patients with anterior and more with inferior infarction. Generally, it is the patient with anterior infarction who provides the principal source of mortality from pump failure in acute myocardial infarction. It is of interest that the study found no significant difference in mortality between treated and control groups of patients with anterior infarction.

Of principal concern are the documentation of the precise type of patient treated and the equality of the prognostic groupings before treatment so that the conclusions on reduction of mortality can be accepted as valid. The patients were selected for study on the basis of Killip class II designation. The presence of rales over less than 50 percent of the lung fields was the criterion for study. In addition, chest X-ray studies were performed in some patients to determine heart size and distribution of pulmonary flow. We do not know whether these films were bedside studies (with resultant distortion of heart size as defined by conventional X-ray criteria). Nevertheless, no significant change of heart size was reported in the treated group. It is well known that chest X-ray criteria for "heart failure" do not necessarily correlate with hemodynamic findings obtained at the same time. No hemodynamic measurements were performed in these patients. This is a serious omission because the most accurate prognostic groupings in acute myocardial infarction come from measurements of the "wedge" pressure and cardiac output,[14,15] which have a relatively poor correlation with rales over less than 50 percent of the lung fields. Simply put, if one uses pulmonary rales as a criterion for study, the prognostic groupings in such a study may vary widely before the institution of the treatment. Whereas these patients were randomized to some extent, the criteria used were not in accordance with current knowledge concerning the most precise means of arriving at a prognosis.

Results of Intraaortic Balloon Pumping

The idea of intervening in acute myocardial infarction in patients with lesser degrees of cardiac dysfunction than in those already in shock is a good one whose time has come because of the very high mortality rates of the shock syndrome. Analysis of reported results of intraaortic balloon pumping once the patient has experienced shock after acute infarction shows a survival rate ranging widely from 11 percent[16] to an optimistic 71 percent.[3] Our own results are in keeping with the lower figure cited. To account for these large differences in reported efficacy of balloon pumping, one can reasonably conclude that differences in the criteria used to define shock are the cause of the differences in results and that results are poorer in patients in whom shock is defined rigidly.

One study[17] compared the results of intraaortic balloon pumping and early coronary bypass surgery in patients with cardiogenic shock. There was a rather low hospital mortality rate for this syndrome in both groups (52 percent for the 21 patients with balloon pumping alone and 42 percent for the 19 patients with balloon pumping followed by early coronary bypass grafting) and no significant difference between the two groups. However, results were better in patients undergoing bypass surgery within 16 hours of symptoms of infarction than in those undergoing later surgery. Longer-term survival rates (6 to 42 months) were apparently more favorable in the surgical group. Mortality rates were considerably lower in patients with "inferior infarction" (could they have had right ventricular infarction?) than in those with anterior infarction. The two groups were not randomly selected so it is possible that there were biased selection criteria and that patients at apparently greater risk were rejected for surgery. All the patients studied had "early" shock. None had shock at the time of admission. In addition, the protocol indicates that the patients responded to treatment with vasopressors, attaining an arterial pressure of 100 mm Hg. These patients must be con-

ANTIBIOTIC PROPHYLAXIS FOR BACTERIAL ENDOCARDITIS

We read the letter about failure of antibiotic prophylaxis of infective endocarditis[1] with concern. These eminent signatories solicit case reports of apparent failure of antibiotic prophylaxis. Surely this is the least important aspect of a very important subject. The authors are seen to be straining after a gnat.

It is only too evident that bacterial endocarditis is not being prevented.[2] Otherwise we would not continue to see infections by the always penicillin-sensitive viridans streptococci with undiminished frequency in our country and in only slightly reduced numbers in yours. Why? (1) Is antibiotic prophylaxis not being given to the right people? (2) Is it not being given? (3) Doesn't it work? (4) Perhaps this is not the problem.

More than 90 percent of our own urgent aortic valve replacements are carried out for viridans streptococcus infection in young men with "bicuspid" aortic valves. Neither they nor their doctors had previously known of the existence of an abnormality.[3] Some may previously have had only a click or no abnormal physical signs to show for it (even had they chanced to see a cardiologist) and they had not been in line for prophylaxis. Few, incidentally, gave a history of recent dental work. It is well known but not emphasized that, although certain abnormalities are more susceptible to infection than others,[4] normal hearts are not immune—and normal hearts are more numerous than abnormal hearts.

Most dental extractions are done outside the hospital and under local anesthesia. Durack himself, when he was in Oxford, carried out a survey which showed that prophylaxis was only given in the (then) recommended way by 8 percent of the local dentists but this was not because of ignorance of what should have been done.[5] Parenteral prophylaxis will never work in England except in hospital dental practice because our dentists do not have the equipment for or nurses to give intramuscular injections. It is logistically almost impossible for a patient to establish a liaison between doctor and nurse in one place and the dentist in another toward the goal of an injection 1 hour before the extraction.

The link between dental extraction (or other work) and endocarditis is conjectural, based on common sense but not on evidence. Low grade bacteremia may occur even during chewing or defecation. As with diseased and normal hearts severe bacteremia may be more dangerous but low grade bacteremia is more frequent.

We make the following suggestions:

(1) Because susceptible individuals cannot be recognized, prophylaxis should be given to everyone before predictable heavy bacteremia. (2) Prophylaxis should be easy or it will not be given. The American Heart Association recommendations are impracticable. We have advocated administration of oral amoxycillin, 3 g, 1 hour before dental extraction, the drug to be stocked by the dentist and handed out to all patients before extraction, sealing or major fillings. Patients who give a history of penicillin sensitivity should receive 2 g of erythromycin also orally.

Shanson et al.[6] have shown and we have confirmed in our hospital that amoxycillin prevents bacteremia after dental extraction. Our dental department finds this drug easy to administer and very acceptable to patients. Patients having general anaesthetic agents should of course be given intramuscular penicillin and gentamicin but they will normally always be in a hospital or clinic where an injection causes no difficulty. The same considerations apply to patients undergoing other bacteremia-producing procedures that are normally carried out in the hospital and in whom appropriate intramuscular antibiotic agents should be given as recommended by the American Heart Association.

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REPLY

We agree that the unanswered questions on prophylaxis of bacterial endocarditis are legion, and have repeatedly taken pains to point this out.[1–4] The AHA Prophylaxis Failure Registry represents a modest attempt to gather information on one of these questions: Do *any* prophylaxis failures occur among susceptible patients receiving antibiotic drugs for attempted prophylaxis of endocarditis? So far, we have received notification of 23 apparent prophylaxis failures, most after treatment with oral penicillin. These cases are currently being analyzed and the data will be reported.

The suggestion that *all* patients undergoing common dental procedures should receive antibiotic prophylaxis for endocarditis is unprecedented. Lest anyone take it too seriously, we offer the following simple cautionary notes:

1. Any proposal to administer *any* drug to *large numbers of normal people* should be critically examined before it is recommended or adopted. Apart from vaccines, vitamins and antimalarial drugs, there is no precedent for indiscriminately giving drugs to normal people. What is the risk-benefit ratio? This probably cannot be calculated, and adverse reactions, possible resulting increase in resistance of normal flora to the penicillins, monetary costs and the need for properly informed patients consent must all be considered.

2. Anaphylactic reactions to oral penicillin are well described, and are occasionally fatal.[5,6] Among 28 cases reviewed by Batson,[5] 13 patients (46 percent) had no previous history of penicillin allergy, most reacted to the first oral dose of penicillin and 2 patients died. *Res ipsa loquitur.*

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MEDICAL VERSUS SURGICAL TREATMENT FOR BACTERIAL VEGETATIONS

Stafford et al.[1] described the disappearance, after medical treatment, of bacterial vegetations diagnosed with serial M mode or two dimensional echocardiography. Two of their six patients had cerebral embolization. One had features of aortic vegetation prolapsing into the left ventricle.

The authors state that it is difficult to detect these changes because most of the patients with vegetations required early valve replacement for intractable heart failure.

I believe that the true question is whether medical treatment alone is sufficient for a patient with bacterial vegetations diagnosed with echocardiography, particularly when these vegetations are shown to be mobile on two dimensional echocardiography or are prolapsing into the left ventricle.

I believe that it is not sufficient. At present, the risk of surgery in active endocarditis is about 10 or 15 percent.[2] The risk of embolization from a bacterial vegetation is totally unknown. Moreover, cerebral embolism is an obstruction to extracorporeal circulation.

In our institution, the discovery of bacterial vegetations on echocardiography is an indication for emergency surgery. If apyrexia can be achieved in the preceding 24 or 48 hours, the result of surgical treatment is better, but even if it is not achieved, I believe that surgical treatment is necessary in these cases.

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REPLY

Roux apparently believes that all patients with vegetations visualized on echocardiography and particularly those with mobile vegetations should be subjected to early valve replacement to prevent cerebral embolization. This unsupported contention is contrary to our experience[1,2] and to that of others.[3] Although the visualization of a vegetation on echocardiography is a poor prognostic sign, a substantial number of patients with this finding do well with medical therapy alone. It is hazardous to base a prediction of outcome solely on the echocardiographic appearance of a vegetation. Proper management of patients with vegetations must continue to be based on clinical integration of multiple factors. Intractable congestive heart failure remains the primary indication for emergency valve replacement. Prevention of cerebral embolization is as yet an unproved indication for valve replacement. Both patients in our medically treated series who had cerebral emboli did quite well and sustained little permanent neurologic impairment. The role of echocardiography in predicting the natural history of embolization due to infective endocarditis and its effect on treatment planning remain to be established. It is premature to recommend immediate valve replacement for all patients with echocardiographically visible vegetations.

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The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

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Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

DECEMBER 1980 THROUGH MARCH 1981

1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

DEC. 4–6 — **Two-Dimensional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director and Leonard S. Dreifus, FACC and Gerald M. Pohost, FACC, co-directors. The Franklin Plaza Hotel, Philadelphia, PA

DEC. 7–10 — **Coronary, Hypertensive, Valvular and Myocardial Heart Diseases: The Multi-Disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 12–14 — **Cardiovascular Disease: Achievements and Challenges 1980.** Henry I. Russek, FACC, director, Sheraton Centre, New York, NY

1981

JAN. 12–16 — **Twelfth Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Opticon Theatre, Snowmass Resort, Snowmass, CO

FEB. 2–4 — **Clinical Echocardiography 1981—M-Mode, 2-Dimensional and Pulsed Doppler Techniques,** Pravin M. Shah, FACC, director and John S. Child, FACC, Joseph K. Perloff, FACC, and Maylene Wong, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

FEB. 9–11 — **Calcium (Slow Channel)-Inhibiting Drugs in Cardiovascular Therapy: Mechanism of Action and Application.** Borys Surawicz, FACC and Attilio Maseri, FACC, directors. New Orleans Marriott, New Orleans, LA

FEB. 19–20 — **Ventricular Arrhythmias and Sudden Cardiac Death.** Thomas B. Graboys, FACC and Bernard Lown, FACC, directors. Sheraton Boston Hotel, Boston, MA

MAR. 30–APR. 3 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Krannert Institute of Cardiology, Indiana University Medical Center, Indianapolis, IN

APR. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 16–18 — **New Diagnostic and Therapeutic Modalities in Cardiology.** Edmund H. Sonnenblick, FACC and James Scheuer, directors. Grand Hyatt New York, New York, NY

APR. 23–24 — **Contemporary Phonocardiography.** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, IN

APR. 27–MAY 1 — **Consultant's Course in Cardiology.** Richard Gorlin, FACC, Louis E. Teicholz, FACC, Simon Dack, FACC and Ephraim Donoso, FACC, directors. Mount Sinai Medical Center, New York, NY

APR. 29–MAY 1 — **Vectorcardiography—An Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

MAY 7–9 — **The Pathology of Acquired Heart Disease and of the Conduction System.** Jesse E. Edwards, FACC, Maurice Lev, FACC and Saroja Bharati, FACC, directors. Radisson Hotel, St. Paul, MN

MAY 7–9 — **Cardiovascular Emergencies.** Arthur Selzer, FACC and Richard Pasternak, co-directors. The Mark Hopkins, San Francisco, CA

MAY 7–9 — **Practical Cardiology for the Primary Care Physician,** Leonard S. Dreifus, FACC and Joel Morganroth, FACC, directors. Sarasota Hyatt Hotel, Sarasota, FL

MAY 13–15 **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. de Leon, Jr., FACC and John F. Stapleton, co-directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington DC

MAY 14–16 **Cardiac Diagnostic Techniques—A Clinical Perspective.** Arnold M. Weissler, FACC and Nicholas Z. Kerin, FACC, directors and Franklin E. Hull, FACC, S. C. Khullar, FACC and Melvin Rubenfire, FACC, co-directors. Detroit Plaza Hotel, Renaissance Center, Detroit, MI

MAY 18–22 **Modern Cardiology.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Sheraton Atlanta Hotel, Atlanta, GA

MAY 28–31 **Sixth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Carillon Hotel, Miami Beach, FL

JUNE 17–19 **The Patient with Arrhythmia—A Clinical Approach.** Ross D. Fletcher, FACC and W. Proctor Harvey, FACC, directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington, DC

JUNE 30–JULY 3 **Eighth Annual Symposium on Clinical Echocardiography: Current Applications and New Developments.** Arthur D. Hagan, FACC, director and Anthony N. DeMaria, FACC and William F. Friedman, co-directors. Snowbird Conference Center, Snowbird Ski and Summer Resort, Snowbird, UT

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rogram lumber	Date	Program Director	Title of Program
308	January 12–13	William Grossman, MD	The Role of the Cardiac Catheter in the Patient with Heart Disease
309	January 15–16	Winston E. Guam, MD and Samuel Kaplan, MD	Cardiac Electrophysiology and Rhythm Disorders in Pediatrics
334	February 5–6	August M. Watanabe, MD	Fundamental Cardiac Biochemistry for the Cardiologist
333	February 12–14	H. J. C. Swan, MD	Newer Concepts and Directions in the Treatment of Heart Failure Associated with Coronary Heart Disease
310	February 16–18	Sylvan Lee Weinberg, MD	Clinical Update for Nurses: The Coronary Care Unit and Acute Myocardial Infarction
311	February 23–25	William C. Roberts, MD	Congenital Heart Disease: The Multidisciplinary Approach
312	March 2–4	Nanette K. Wenger, MD	Rehabilitation of the Cardiac Patient
313	March 30–31	Jere H. Mitchell, MD	Cardiovascular Benefits and Risks of Exercise
314	April 1–3	J. O'Neal Humphries, MD	Coronary Heart Disease: New Management Methods
315	April 8–10	Victor Parsonnet, MD	Current Concepts in Pacing
316	April 13–15	Keith Cohn, MD	Exercise Testing: Diagnostic and Physiological Considerations
317	April 20–22	Pravin M. Shah, MD	Current Applications of Echocardiography: M-Mode, Two-Dimensional and Pulse Doppler Techniques
318	April 23–25	Daniel S. Berman, MD	Nuclear Cardiology
319	April 27–28	Leonard S. Dreifus, MD and Frits L. Meijler, MD	Computer Electrocardiology: Present Status and Hope for the Future
320	April 30, May 1–2	John A. Spittell, MD	Peripheral Vascular Disease
321	May 6–8	Marvin I. Dunn, MD	Electrocardiography for Critical Care Nurses
322	May 11–13	Abdul J. Tajik, MD and James B. Seward, MD	The Role of Two-Dimensional Echocardiography in the Clinical Practice of Cardiology
323	May 14–16	G. Charles Oliver, MD	Ubiquitous PVC
324	May 18–20	William J. Mandel, MD	His Bundle Electrocardiography: Contributions to the Clinical Understanding of the Electrocardiogram
325	May 28–29	Robert O. Brandenburg, MD	Cardiology for the Consultant
326	June 1–3	Shahbudin H. Rahimtoola, MD	Valvular Heart Disease
328	June 8–10 (tentative)	Borys Surawicz, MD	Changing Role of Electrocardiography in the Clinical Practices
327	June 11–13	Robert G. Tancredi, MD	Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients
329	June 15–17	Robert A. O'Rourke, MD	Detection of Cardiac Disease by Physical Examination
302	June 22–24	Paul C. Gillette, MD	Decisions in Clinical Pediatric Cardiac Surgery
331	June 29–30, July 1	B. Leonard Holman, MD	Nuclear Cardiology
330	July 8–10	Michael R. Rosen, MD	Clinical Pharmacology and Electrophysiology of Antiarrhythmic Drugs

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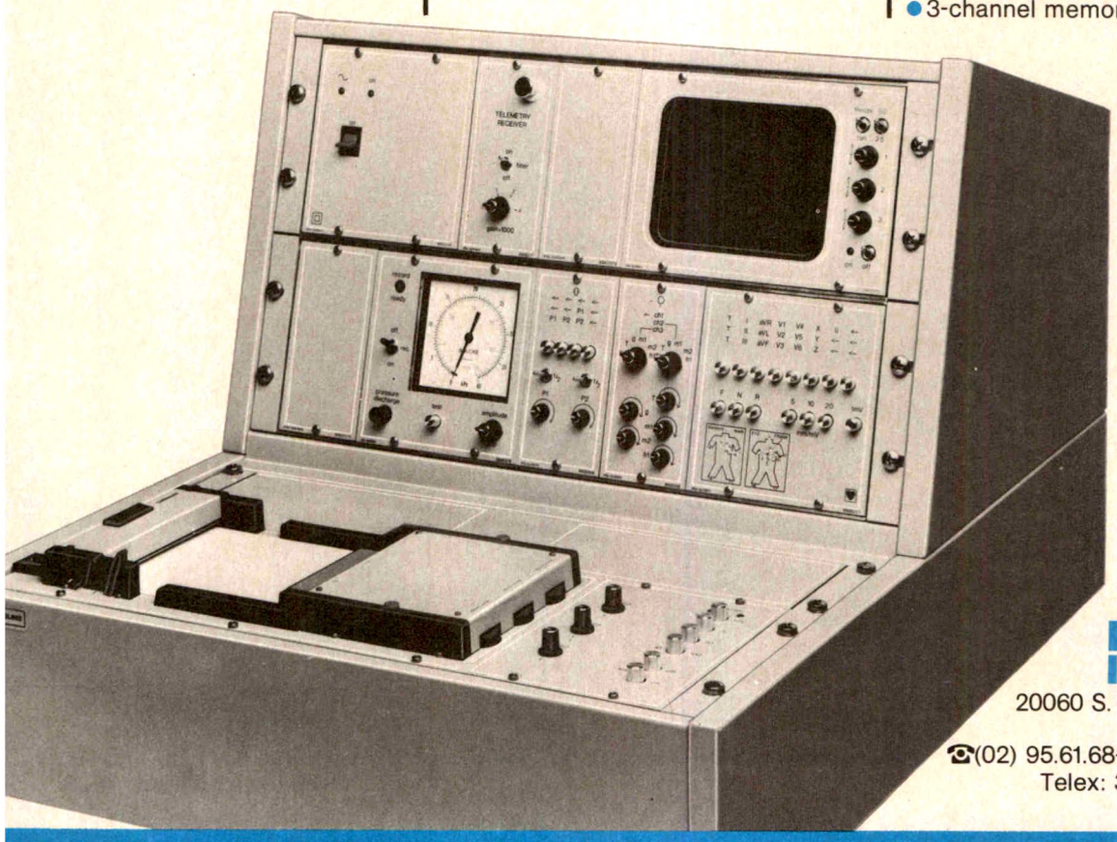


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onsider Inderal: It reduces heart rate—therapeutically—by some 12 eats a minute.[1-6] 720 fewer beats per hour. Some 6 million fewer beats er year. That means less work for the anginal heart. Less oxygen emand by the myocardium. Fewer anginal attacks. Less need for ublingual nitroglycerin. More tolerance for exercise—and more reedom of action.

eduction in heart rate is modest: should not be cause for concern.[7] he relatively low dosages required for angina prophylaxis (an average f 160 mg/day) produce few, if any, serious adverse reactions, which n any case are readily recognized and controlled.

/ith proper patient selection—in the absence of bronchial asthma, inus bradycardia, or heart block greater than first degree—risk of recipitating cardiac failure is extremely rare. And withdrawal prob-ems may be avoided by reducing dosage gradually—rather than bruptly.*

onsider too: There is also a favorable redistribution of perfusion to ne vulnerable subendocardium.[8] And, in patients who may still need itroglycerin p.r.n., INDERAL will cancel the undesirable increase n heart rate and contractility.

rescribe INDERAL with confidence. Effec-ve. Reliable. For patients with moder-te to severe angina in whom conven-onal measures have failed.

r full information on Contraindications, Precautions, Adverse Reac-ns, and Warnings, including avoidance of abrupt withdrawal, please sult the prescribing information on the following page.

INDERAL®
(PROPRANOLOL HCl)
TODAY'S BENCHMARK FOR **ANGINA**
40mg 80mg tabs.

Ayerst

H[illegible]

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® BRAND OF
PROPRANOLOL HYDROCHLORIDE
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis: The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONC EMPHYSEMA), INDERAL should be administered with caution since it may block bronch tion produced by endogenous and exogenous catecholamine stimulation of beta recept

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adre blocking activity, INDERAL may prevent the appearance of premonitory signs and symp (pulse rate and pressure changes) of acute hypoglycemia. This is especially important t in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by cipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been es tablished. Use of any drug in pregnancy or women of childbearing potential requires tha possible risk to mother and/or fetus be weighed against the expected therapeutic bene bryotoxic effects have been seen in animal studies at doses about 10 times the maximur ommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely served if INDERAL is administered. The added catecholamine blocking action of this dr then produce an excessive reduction of the resting sympathetic nervous activity. Occas the pharmacologic activity of INDERAL may produce hypotension and/or marked brad resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be served at regular intervals. The drug should be used with caution in patients with impair or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypot paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytope purpura

Central Nervous System: lightheadedness; mental depression manifested by insomni tude, weakness, fatigue; reversible mental depression progressing to catatonia; visual d bances; hallucinations; an acute reversible syndrome characterized by disorientation fo and place, short term memory loss, emotional lability, slightly clouded sensorium, and d creased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea stipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with ac and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic pu

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the ski ous membranes and conjunctivae reported for a beta blocker (practolol) have not been sively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe h ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three o times daily, before meals and at bedtime, dosage should be gradually increased at thre seven day intervals until optimum response is obtained. Although individual patients ma spond at any dosage level, the average optimum dosage appears to be 160 mg per da angina pectoris, the value and safety of dosage exceeding 320 mg per day have not be established.

If treatment is to be discontinued, reduce dosage gradually over a period of several w (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit a quate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWIN SURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESP TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THE EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. T adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

References: 1. Dagenais, G.R., Pitt, B., and Ross, R.S.: Am. J. Cardiol. *28*:10 (July) 197 2. Ginn, W.M., and Orgain, E.S.: J.A.M.A. *198*:192 (Dec. 12) 1966. 3. Zeft, H.J., Patterso and Orgain, E.S.: Arch. Intern. Med. *124*:578 (Nov.) 1969. 4. Dunér, H., and Pernow, B.: Med. Scand. *194*:517 (Dec.) 1973. 5. Zsotér, T.T., and Beanlands, D.S.: Arch. Intern. Me *124*:584 (Nov.) 1969. 6. Wiener, L., Dwyer, E.M., and Cox, J.W.: Circulation. *39*:623 (Ma 7. Shand, D.G.: Drug Therapy *8*:53 (July) 1978. 8. Cohen, L.S., in Braunwald, E. (ed): B Adrenergic Blockade, A New Era in Cardiovascular Medicine: Proceedings of an Intern Symposium, New York, Excerpta Medica/Elsevier, 1978, pp. 143-151.

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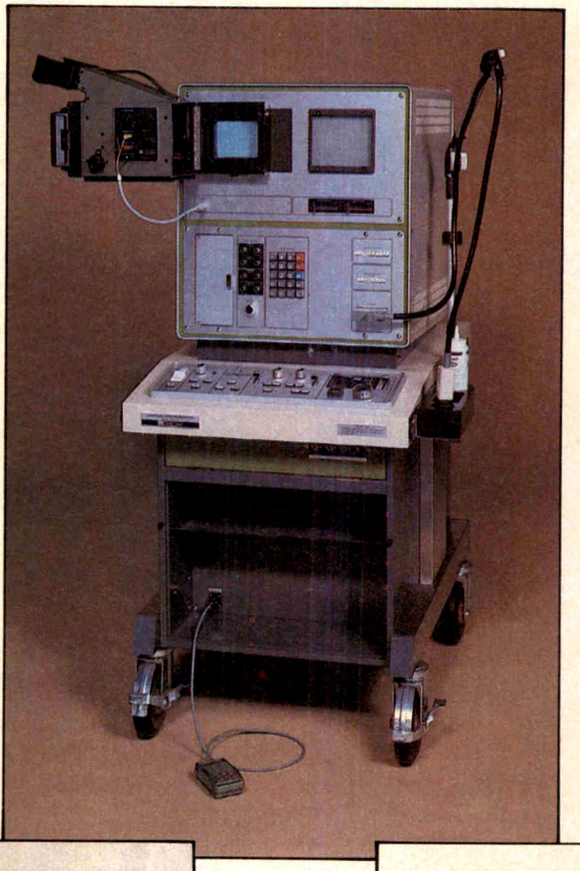
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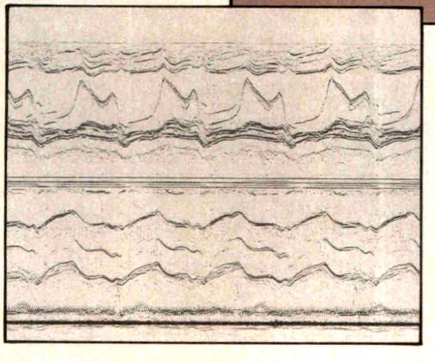
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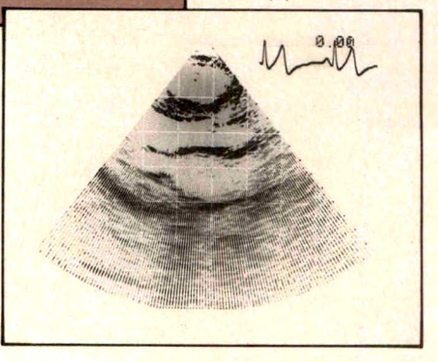
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Left: Dual channel M mode showing simultaneously aorta and mitral function.

Right: Long axis left heart.



TOSHIBA
MEDICAL SYSTEMS

Time is the test of all things.

1954
1980



BRIEF SUMMARY

Kaon® Elixir (potassium gluconate) Grape or Lemon-Lime Flavo
Sugar-Free

Description: Each 15 ml (tablespoonful) supplies 20 mEq of elemental (as potassium gluconate, 4.68 g) with saccharin and aromatics. Alcohol

Indications: Kaon Elixir is indicated for the treatment of potassium dep patients with hypokalemia and for the treatment of digitalis intoxication. Elixir is also indicated for the prevention of potassium depletion when th intake of potassium is inadequate for this purpose. The prophylactic adm of potassium ion may be indicated in patients receiving digitalis and diuret treatment of congestive heart failure; hepatic cirrhosis with ascites; patients hypertension on long-term diuretic therapy; patients on corticosteroid therap hyperaldosteronism states with normal renal function; the nephrotic syndrom certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients wit kalemia since a further increase in serum potassium concentration in such patients produce cardiac arrest. Hyperkalemia may complicate any of the following condition renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive breakdown as in severe burns, adrenal insufficiency, or the administration of a potassiu diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation tered undiluted. For details regarding adequate dilution, see Dosage and Administration.

In patients with impaired mechanisms for excreting potassium, the administration of potassiu produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemi develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly car monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium and a potassium-sparing diuretic (e.g. spironolactone or triamterene) since the simultar administration of these agents can produce severe hyperkalemia.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrati hypokalemia in a patient with a clinical history suggesting some cause for potassium de tion. In interpreting the serum potassium level, the physician should bear in mind that alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium conc tion into the normal range even in the presence of a reduced total body pota sium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to a base balance and appropriate monitoring of serum electrolytes, the el cardiogram, and the clinical status of the patient.

In hypokalemic states, especially in patients on a low-salt di hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In the circumstances, potassium replacement with potassiu chloride (e.g. Kaochlor 10% Liquid, W-T) may be advantageous than with other potassium salts. Ho Kaon can be supplemented with chloride. Ammon chloride is an excellent source of chloride ion (18.7 per gram) but it should not be used in patients with he cirrhosis where ammonium salts are contraindicated.

Adverse Reactions: Nausea, vomiting, diarrhea, a abdominal discomfort have been reported. The sy toms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis listlessness, mental confusion, weakness and iness of the legs, fall in blood pressure, cardia rhythmias, and heart block.

Overdosage: The administration of oral pot salts to persons with normal excretory mechan for potassium rarely causes serious hyperkalem However, if excretory mechanisms are impaired potassium is administered too rapidly intravenousl tentially fatal hyperkalemia can result (see Contraind tions and Warnings). It is important to recognize that hy kalemia is usually asymptomatic and may be manifested only increased serum potassium concentration and characteristic electrocardi graphic changes (peaking of T-waves, loss of P-wave, depression of S-T ment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

How Supplied: Pints and gallons in Grape and Lemon-Lime flavors; 1 Stat-Pak® and 4 fl. oz. in Grape flavor only.

Kaon® Elixir
(potassium gluconate)
20 mEq per 15 ml

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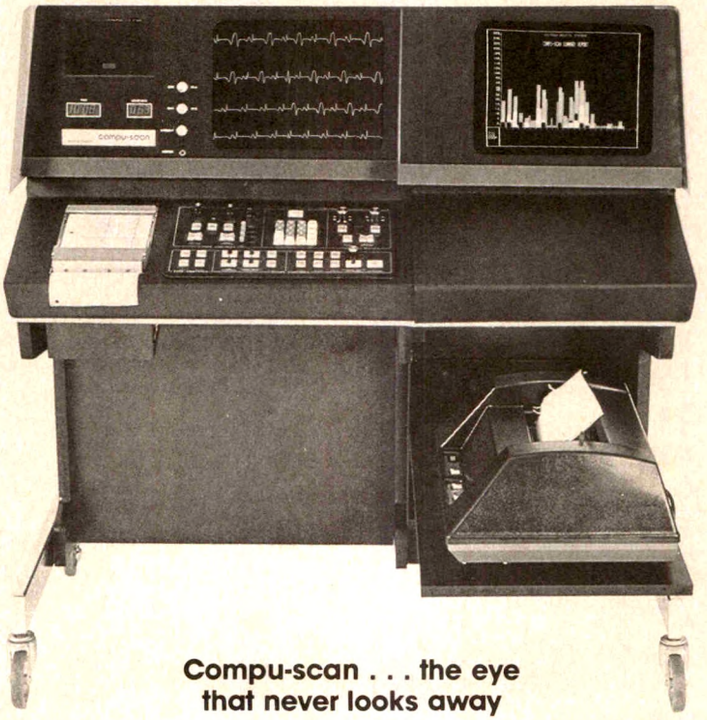
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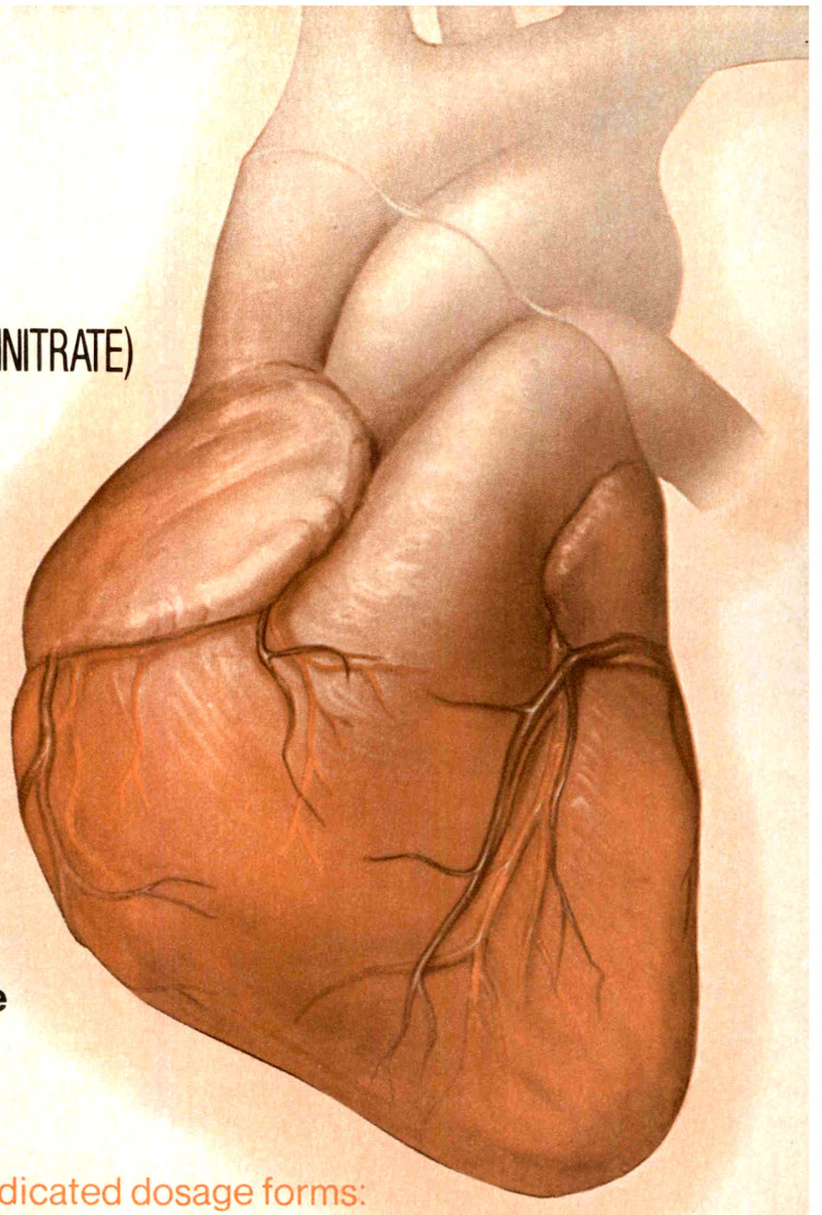
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Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

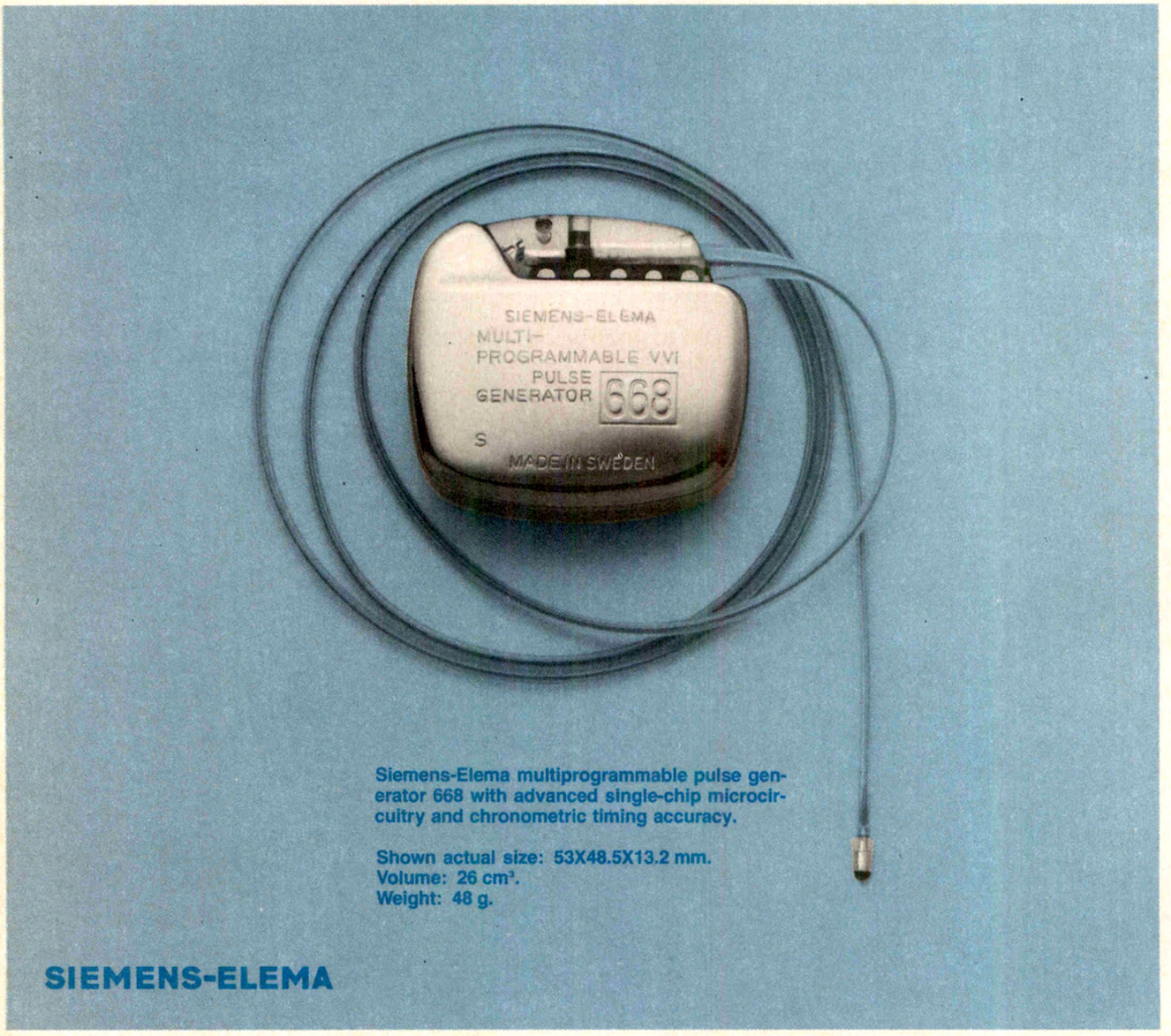
Consult direction circular before prescribing.

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STATE OF THE ART:



Siemens-Elema multiprogrammable pulse generator 668 with advanced single-chip microcircuitry and chronometric timing accuracy.

Shown actual size: 53X48.5X13.2 mm.
Volume: 26 cm³.
Weight: 48 g.

SIEMENS-ELEMA

Perhaps never before has there been a pacing system so responsive to your needs.

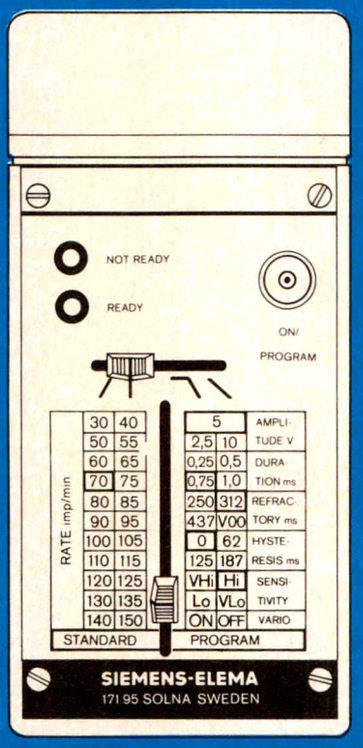
With six programmable parameters (including amplitude as high as 10 V) and the Vario® function, the versatile 668 generator offers more than 30,000 operating combinations.

The exclusive Vario function permits easy determination of stimulation threshold—a check readily performed by support staff as part of standard routine.

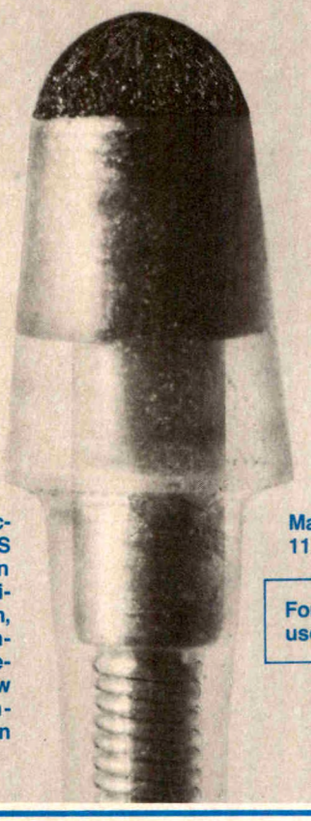
The Type 411S low-threshold, vitreous-carbon lead tip promises extended generator service life and an end to complications such as exit block and sensing

THE COMPLETE MULTIPURPOSE PACING SYSTEM

THE MULTIPROGRAMMABLE PULSE GENERATOR 668.
FROM SIEMENS-ELEMA—THE PEOPLE WHO PIONEERED
THE FIRST IMPLANTABLE PACEMAKER IN 1958.



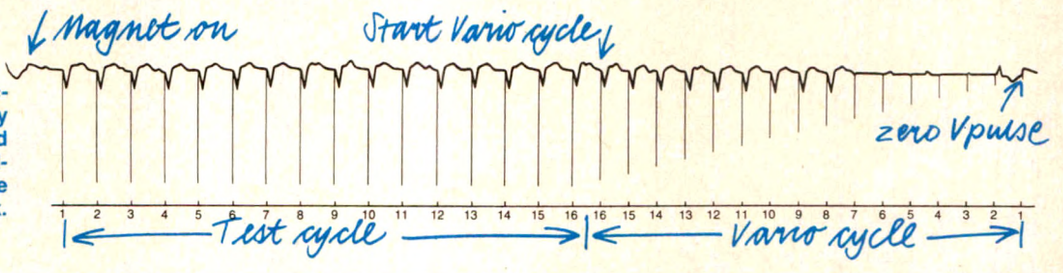
Programming unit for 668 generator features simple and straightforward operation, can also be used as pulse generator test magnet.



The porous character of the Type 411S vitreous-carbon lead tip inhibits fibrotic tissue growth, common with conventional tip materials, permitting low initial and maintained stimulation threshold.

Magnified 11X

For clinical use only



Plot of Vario function displays battery test cycle initiated by test magnet followed by Vario cycle for threshold check.

80214

difficulties often associated with conventional electrode materials.

All this, coupled with Siemens-Elema's superb record of reliability, suggests that the 668 pulse generator used with the Type 411S carbon-tip lead truly defines the state of the art.

Please write for specifications and clinical data.

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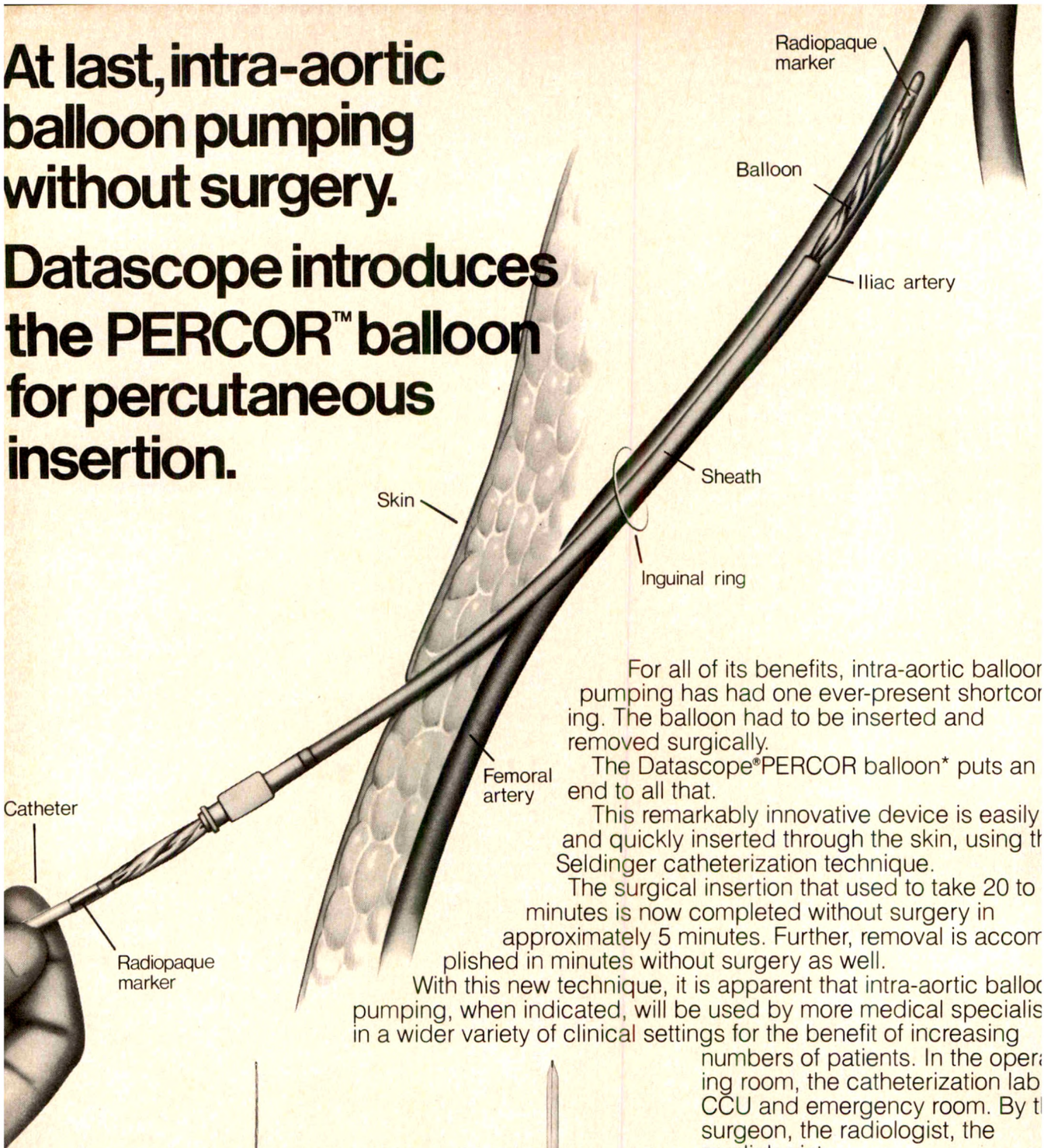
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Clinical reference: *Preliminary Clinical Experience With Percutaneous Intra-Aortic Balloon Pumping (IABP)*, V. A. Subramanian, Jonathan Goldstein Thomas A. Sos, John C. McCabe, Eddie Hoover & William A. Gay, Jr., New York Hospital, New York, NY. Abstract published in CIRCULATION, Part I

"Doc, how about throwing out your Holter service? My new micro-processor based recorder gives you only the beats you want...the really sick ones."



"Hmmm... hard to believe..."

Rep: No, no, you don't understand. Our machine has been preprogrammed to record only the *abnormal* beats. Why waste time with all the unimportant stuff?

"Doc:" I *do* understand...and *I* like to be the one to decide what's important; to decide what's clinically significant or insignificant.

Rep: But...

"Doc:" How can I be sure that thing records all I want to see? What happens to all the *un*recorded heartbeats? I'm supposed to accept what your micro-processor records on blind faith, right?... *Wrong!*

Rep: Saaay!... why don't we fly you right out here for a little business vacation...y'know, a little fun, take a look at the product...

"Doc:" I *also* like to decide when and where I'll vacation. Why can't you just send a salesman?

Rep: Salesman? Whaaat salesman? These things sell *themselves,* Doc. Our recorders monitor up to two, that's *two* full hours of significant cardiac events. I mean, a patient with any more trouble than that...what's the *point,* y'know?

"Doc:" Saaay!...would you like to hear a really unusual sound?

Rep: Uh...sure.

"Doc:" (CLICK)

Now we're not saying that there aren't some awfully spiffy micro-technological miracles in new Holter recording devices out there.

We're just asking you to *be careful.* Be ready. Ask the *tough* questions. About too-good-to-be-true performance claims, options, and confounding complications. And don't forget to demand a "show me," hands-on demonstration.

And remember...those far-away seminars and demonstrations can mean far-away delivery and far-away service facilities.

At Clinical Data, you don't have to ask a lot of questions about a lot of complicated contingencies. Just one simple question: does Clinical Data give you a state-of-the-art, comprehensive, quality-controlled, readable, long-term ECG report? With accurate data, clearly reported?

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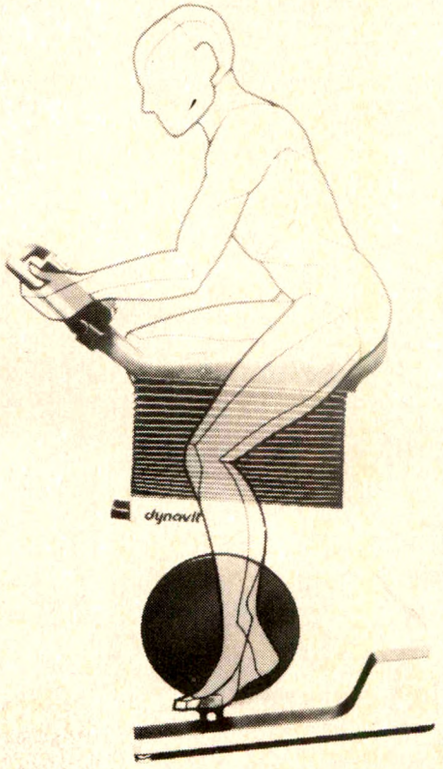
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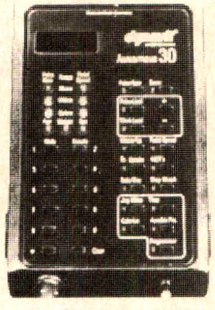
A 109

A dynamometer which measures physical work rates

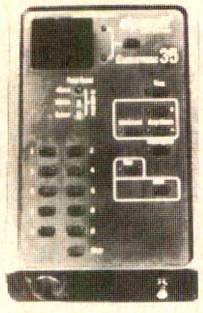


Now with the new series of Dynavit equipment, graded exercise is possible on an ergometer with its own built-in calibrating dynamometer. Controlled pulses of current are fed through electrical windings of the braking system and a magnetic field is induced which becomes the braking torque to oppose the flywheel's rotation. The braking system is float mounted such that it responds in a counter torsion movement, and this is mechanically transmitted into a precision strain gauge.

And a phototachometer accurately counts the flywheel revolutions per minute. Therefore, the true and effective cranking effort (work rate = watts of power expended) is dynamometrically controlled. **Constant, calibrated and controlled work rates independent of pedal speed!**



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West Germany

Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

NOTE: The CyberLith and the CyberLith Programmer are currently undergoing clinical evaluation.

Intermedics Inc.
Our business is life.™

The CyberLith® programming system.

Reliable, safe, convenient. And available.



yberLith... the most sophisticated ogramming system ever.

eliable

The CyberLith all electronic pro- amming system assures reliability by minating phantom or cross-program- ing. The use of accurate crystal oscilla- rs ensures precision transmission of ogramming information.

fe

The CyberLith programming safety atures help avoid unnecessary cardiac ythm disturbances. Further, it is not cessary to place the pulse generator in e asynchronous mode during the pro- amming session. The safety features also allow automatic error identification, preventing transmission of incompatible programming commands.

Convenient

The CyberLith programming system is fast — all five parameters are programmed within 40 milliseconds.

Available

CyberLith pacing systems are available now! Pulse generators, programmers, leads, telemetry equipment, and patient transmitters and receivers.

As the pioneers of multi-parameter programmable pacing technology, Intermedics has maintained its role as the manufacturer of the most advanced systems. Our commitment is to keep in pace with your desire for excellence in pacing therapy.

The CyberLith system is today's state-of-the-art. Get to know it. For more detailed information call or write the Intermedics marketing department, or contact your local Intermedics representative.

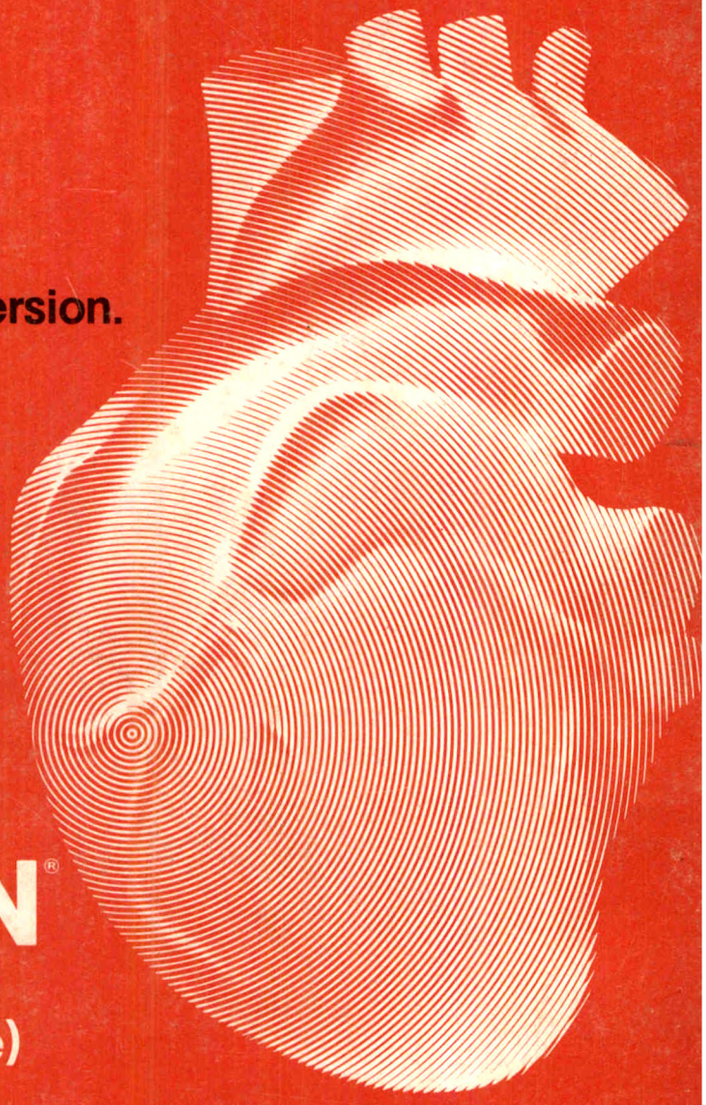
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The Pacekeeper™



For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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DECEMBER 18, 1980

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Symposium: Two Dimensional Echocardiography Versus Cardiac Nuclear Imaging Techniques

Joel Morganroth, MD, FACC

Gerald M. Pohost, MD, FACC

Guest Editors

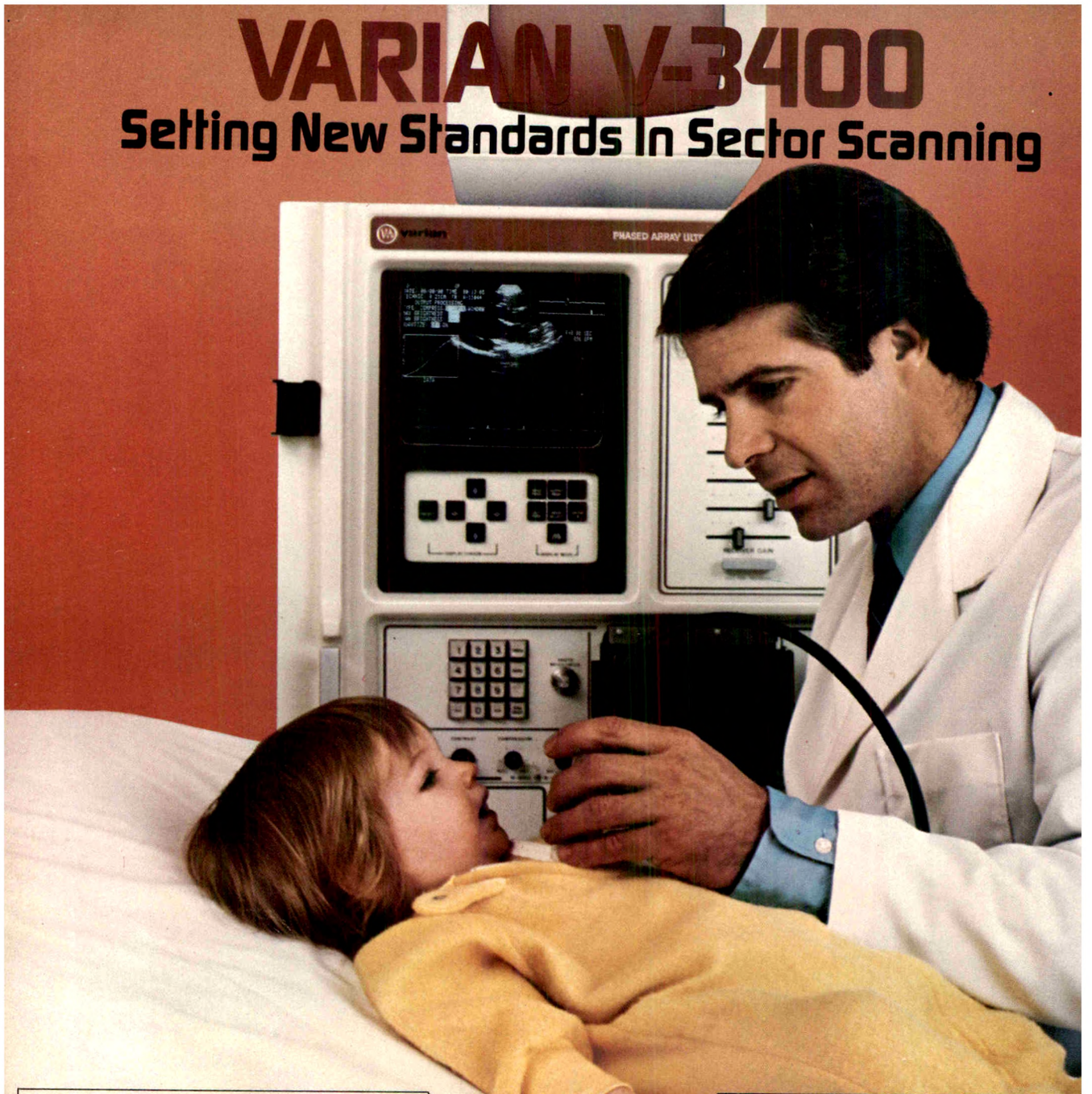
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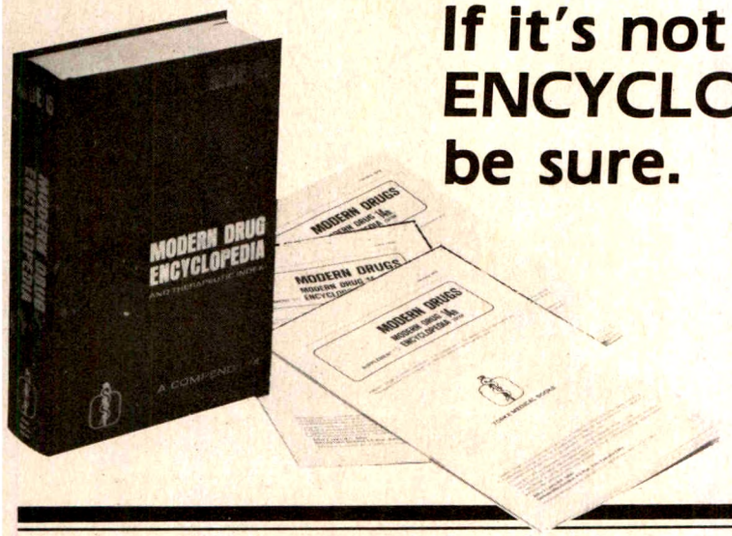
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See brief summary on following page.

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o Nuclear Medicine

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TechneScan® PYP®

Technetium Tc-99m Pyrophosphate Kit

RIEF SUMMARY

NICAL PHARMACOLOGY

en injected intravenously **TechneScan PYP Tc 99m** has a specific affinity for areas ltered osteogenesis. It is also concentrated in the injured myocardium, primarily reas of irreversibly damaged myocardial cells.

to two hours after intravenous injection of **TechneScan PYP Tc 99m**, an estimated o 50 percent of the injected dose has been taken up by the skeleton and approx- tely 0.01 to 0.02 percent per gram of acutely infarcted myocardium. Within a od of one hour, 10 to 11 percent remains in the vascular system, declining to ap- ximately 2 to 3 percent twenty-four hours post injection. The average urinary ex- ion was observed to be about 40 percent of the administered dose after 24 hours.

hneScan PYP also has an affinity for red blood cells. When administered 30 utes prior to the intravenous administration of sodium pertechnetate Tc-99m ap- ximately 76 percent of the injected activity remains in the blood pool providing ex- ent images of the cardiac chambers.

ICATIONS AND USAGE

hneScan PYP Tc 99m is a skeletal imaging agent used to demonstrate areas of red osteogenesis, and a cardiac imaging agent used as an adjunct in the inosis of acute myocardial infarction.

in adjunct in the diagnosis of confirmed myocardial infarction (ECG and serum ymes positive), the incidence of false negative images has been found to be 6 per- t. False negative images can also occur if made too early in the evolutionary phase he infarct or too late in the resolution phase. In a limited study involving 22 pa- ts in whom the ECG was positive and serum enzymes questionable or negative, in whom the final diagnosis of acute myocardial infarction was made, the in- nce of false negative images was 23 percent. The incidence of false positive im- s has been found to be 7 to 9 percent. False positive images have also been orted following coronary by-pass graft surgery, in unstable angina pectoris, old cardial infarcts and in cardiac contusions.

hneScan PYP is a blood pool imaging agent which may be used for gated cardiac od pool imaging. When administered intravenously 30 minutes prior to the in- enous administration of sodium pertechnetate Tc-99m approximately 76 percent he injected activity remains in the blood pool.

NTRAINDICATIONS

e.

RNINGS

radiopharmaceutical should not be administered to patients who are pregnant or ating unless the information to be gained outweighs the potential hazards.

lly, examinations using radiopharmaceuticals, especially those elective in ire, of a woman of childbearing capability should be performed during the first (approximately 10) days following the onset of menses.

ning: Preliminary reports indicate impairment of brain scans using pertechnetate 9m which have been preceded by bone scan. The impairment may result in false itives or false negatives. It is recommended, where feasible, that brain scans ede bone imaging procedures.

iopharmaceuticals should be used only by physicians who are qualified by cific training in the safe use and handling of radionuclides produced by nuclear tor or particle accelerator and whose experience and training have been approv- by the appropriate government agency authorized to license the use of onuclides.

The **TechneScan PYP Kit** must be maintained at refrigerator temperature u

The contents of the **TechneScan PYP** reaction vial are intended for use in t tion of Technetium Tc 99m Stannous Pyrophosphate. **TechneScan PYP** r reconstituted with sterile, pyrogen-free normal saline containing no pr and injected intravenously prior to the administration of sodium pe Tc-99m.

Sodium pertechnetate Tc-99m solutions containing an oxidizing age suitable for use with the **TechneScan PYP Kit**.

The contents of the kit are not radioactive. However, after the sodium perte 99m is added, adequate shielding of the final preparation must be maintai

TechneScan PYP Tc 99m should not be used more than six hours after prep

PRECAUTIONS

As in the use of any other radioactive material, care should be take minimum radiation exposure to the patient, consistent with proper patie ment, and to insure minimum radiation exposure to occupational workers

Bone Imaging

Both prior to and following **TechneScan PYP Tc 99m** administration, pati be encouraged to drink fluids. Patients should void as often as possit **TechneScan PYP Tc 99m** injection to minimize background interferen cumulation in the bladder and unnecessary exposure to radiation.

Cardiac Imaging

Patient's cardiac condition should be stable before beginning the card procedure.

If not contraindicated by the cardiac status, patients should be encourag fluids and to void frequently in order to reduce unnecessary radiation exp

Interference from chest wall lesions such as breast tumors and healing r can be minimized by employing the three recommended projections.

Blood Pool Imaging

TechneScan PYP should be injected by direct venipuncture. Heparinize systems should be avoided.

ADVERSE REACTIONS

None.

HOW SUPPLIED

Catalog Number—*094* **TechneScan PYP Technetium Tc-99m Pyroph**

Kit Contains:

5—Stannous Pyrophosphate Reaction Vials (lyophilized) for the pre Technetium Tc-99m Stannous Pyrophosphate.

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12.0 mg sodium pyrophosphate and 3.4 mg stannous chloride (I Hydrochloric acid is added for pH adjustment prior to lyophilization.

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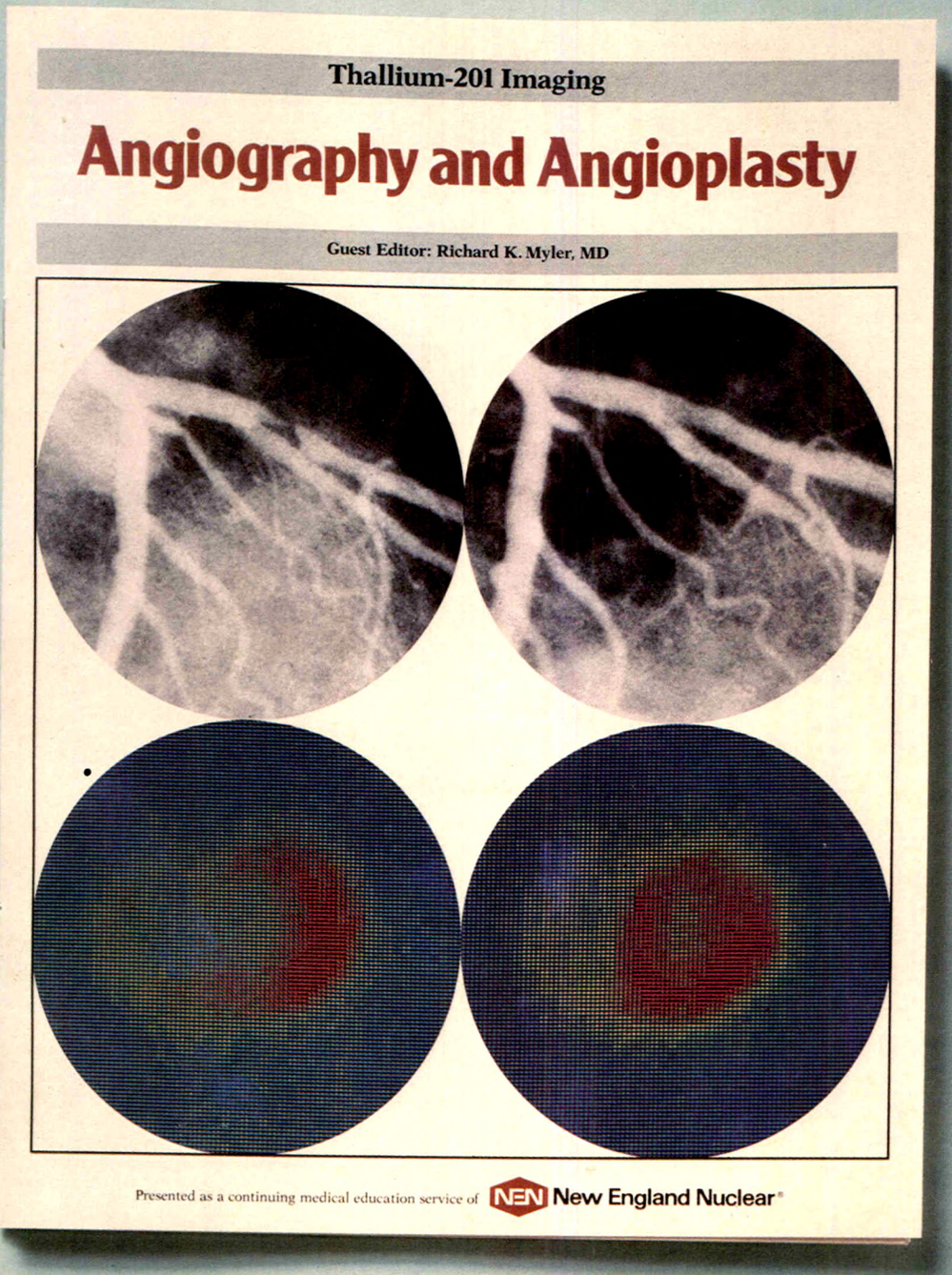
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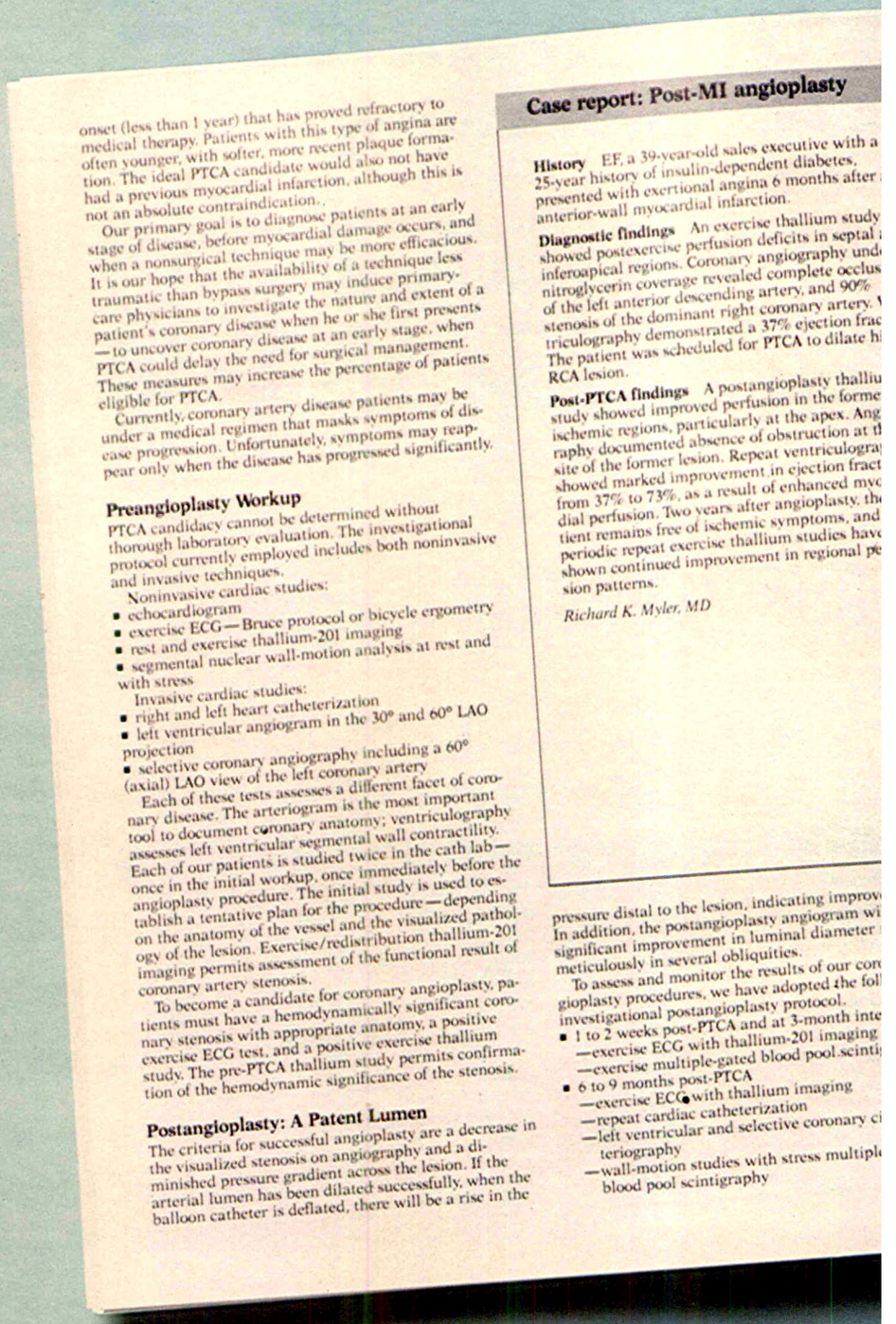
Andreas R. Grüntzig
Richard K. Myler
Simon H. Stertzer

Three leaders in angioplasty discuss patient evaluation, technique, and diagnostic philosophies in an important new monograph. Available without charge from New England Nuclear.



Less invasive evaluation... less traumatic therapy.

As a practicing clinician, you've probably observed with growing interest the new diagnostic and therapeutic techniques for evaluating and managing your coronary artery disease patients. Two of the newest techniques entering routine clinical use hold great promise because they are relatively noninvasive: thallium-201 myocardial perfusion imaging, and percutaneous transluminal coronary angioplasty. Not surprisingly, the thallium-201 study has become a vital tool both in evaluation and followup of all patients being considered for angioplasty.



onset (less than 1 year) that has proved refractory to medical therapy. Patients with this type of angina are often younger, with softer, more recent plaque formation. The ideal PTCA candidate would also not have had a previous myocardial infarction, although this is not an absolute contraindication.

Our primary goal is to diagnose patients at an early stage of disease, before myocardial damage occurs, and when a nonsurgical technique may be more efficacious. It is our hope that the availability of a technique less traumatic than bypass surgery may induce primary-care physicians to investigate the nature and extent of a patient's coronary disease when he or she first presents —to uncover coronary disease at an early stage, when PTCA could delay the need for surgical management. These measures may increase the percentage of patients eligible for PTCA.

Currently, coronary artery disease patients may be under a medical regimen that masks symptoms of disease progression. Unfortunately, symptoms may reappear only when the disease has progressed significantly.

Preangioplasty Workup

PTCA candidacy cannot be determined without thorough laboratory evaluation. The investigational protocol currently employed includes both noninvasive and invasive techniques.

Noninvasive cardiac studies:
- echocardiogram
- exercise ECG—Bruce protocol or bicycle ergometry
- rest and exercise thallium-201 imaging
- segmental nuclear wall-motion analysis at rest and with stress

Invasive cardiac studies:
- right and left heart catheterization
- left ventricular angiogram in the 30° and 60° LAO projection
- selective coronary angiography including a 60° (axial) LAO view of the left coronary artery

Each of these tests assesses a different facet of coronary disease. The arteriogram is the most important tool to document coronary anatomy; ventriculography assesses left ventricular segmental wall contractility. Each of our patients is studied twice in the cath lab—once in the initial workup, once immediately before the angioplasty procedure. The initial study is used to establish a tentative plan for the procedure—depending on the anatomy of the vessel and the visualized pathology of the lesion. Exercise/redistribution thallium-201 imaging permits assessment of the functional result of coronary artery stenosis.

To become a candidate for coronary angioplasty, patients must have a hemodynamically significant coronary stenosis with appropriate anatomy, a positive exercise ECG test, and a positive exercise thallium study. The pre-PTCA thallium study permits confirmation of the hemodynamic significance of the stenosis.

Postangioplasty: A Patent Lumen

The criteria for successful angioplasty are a decrease in the visualized stenosis on angiography and a diminished pressure gradient across the lesion. If the arterial lumen has been dilated successfully, when the balloon catheter is deflated, there will be a rise in the

Case report: Post-MI angioplasty

History EF, a 39-year-old sales executive with a 25-year history of insulin-dependent diabetes, presented with exertional angina 6 months after anterior-wall myocardial infarction.

Diagnostic findings An exercise thallium study showed postexercise perfusion deficits in septal inferoapical regions. Coronary angiography und nitroglycerin coverage revealed complete occlus of the left anterior descending artery, and 90% stenosis of the dominant right coronary artery. triculography demonstrated a 37% ejection frac The patient was scheduled for PTCA to dilate h RCA lesion.

Post-PTCA findings A postangioplasty thalliu study showed improved perfusion in the forme ischemic regions, particularly at the apex. Ang raphy documented absence of obstruction at t site of the former lesion. Repeat ventriculogra showed marked improvement in ejection fract from 37% to 73%, as a result of enhanced myo dial perfusion. Two years after angioplasty, th tient remains free of ischemic symptoms, and periodic repeat exercise thallium studies have shown continued improvement in regional pe sion patterns.

Richard K. Myler, MD

pressure distal to the lesion, indicating improv In addition, the postangioplasty angiogram wi significant improvement in luminal diameter meticulously in several obliquities.

To assess and monitor the results of our cor gioplasty procedures, we have adopted the fol investigational postangioplasty protocol.
- 1 to 2 weeks post-PTCA and at 3-month inte
  —exercise ECG with thallium-201 imaging
  —exercise multiple-gated blood pool scinti
- 6 to 9 months post-PTCA
  —exercise ECG with thallium imaging
  —repeat cardiac catheterization
  —left ventricular and selective coronary c teriography
  —wall-motion studies with stress multipl blood pool scintigraphy

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Historical notes

Andreas R. Grüntzig, MD
University Hospital
Zurich, Switzerland

"Intraoperative experience demonstrated that coronary artery atheroma could be successfully compressed in the living human, and that disruption of the plaque produced no emboli."

Clinical indications and considerations

Richard K. Myler, MD
University of California,
San Francisco Medical School

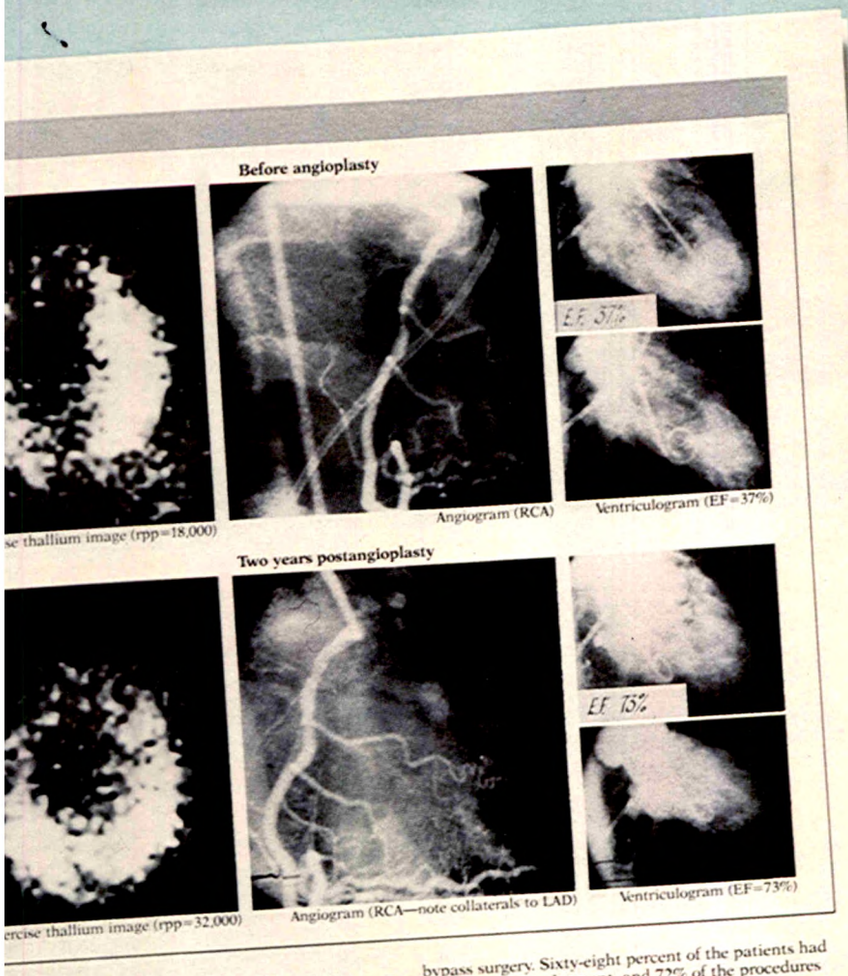
"Patients whose coronary artery disease responds to transluminal angioplasty typically present with severe angina... of recent onset... that has proved refractory to medical therapy."

A clinical primer on technique

Simon H. Stertzer, MD
Lenox Hill Hospital
New York, New York

"Whether the brachial or femoral approach is used for the arteriography depends on the approach to be used for the angioplasty procedure and on the personal preference of the physician."

..and a new monograph on their synergy



years post-PTCA
–exercise ECG with thallium imaging
–repeat cardiac catheterization
–left ventricular and selective coronary cineariography
–multiple-gated blood pool scintigraphy
If symptoms of coronary artery disease reappear, the llowup protocol is altered and selective coronary ariography will be repeated earlier. Patients are maintined on an anticoagulant regimen for 6 months.

esults to Date

the recently reported series of Grüntzig, angioplasty as performed on 129 lesions in 121 patients. The proedure was successful primarily (first procedure) in 100 atients; in 21 patients, the catheter could not be assed. Twelve of the 121 patients required immediate bypass surgery. Sixty-eight percent of the patients had single-vessel involvement, and 72% of the procedures were performed on the left anterior descending artery. The mean pressure gradient after dilatation was reduced from 55 to 19 mm Hg, and the percentage occlusion was reduced from an average of 83 to 36%. Thallium-201 images of all patients with single-vessel disease who underwent successful PTCA showed improved perfusion in regions supplied by dilated arteries. The primary success rate for this series was 78%; including second procedures, the success rate was 93%.

Complications. PTCA is a therapeutic maneuver with a risk of complications. The major complications of the technique are arterial dissection at the angioplasty site, abrupt reclosure (probably caused by spasm), and myocardial infarction.

However, the reported complication rate is relatively

allium-201 and angioplasty: ynergistic diagnostics

ndreas R. Grüntzig, MD
mon H. Stertzer, MD
th
artin E. Bloomfield, MD
nox Hill Hospital

allium imaging gives the ysician another measure of e hemodynamic significance an observed stenosis."

To assist clinicians in determining which of their patients might benefit from these new diagnostic and therapeutic techniques, New England Nuclear has underwritten the development of a new monograph on the synergy of thallium-201 imaging, angiography, and angioplasty. This monograph is available without charge upon request. Simply complete the reply card below and mail it for your copy. A slide program on the subject for teaching rounds use is also available.

☐ Please send me a complimentary copy of the *Angiography and Angioplasty* monograph.

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Thallous Chloride Tl 201

FOR DIAGNOSTIC USE

DESCRIPTION: Thallous Chloride Tl 201 is supplied in isotonic solution as a sterile, nonpyrogenic diagnostic radiopharmaceutical for intravenous administration. The aqueous solution at calibration time contains 1mCi/ml Thallous Chloride Tl 201, adjusted to pH 4.5-6.5 by the addition of hydrochloric acid and/or sodium hydroxide solution. It is made isotonic with 0.9% sodium chloride and is preserved with 0.9% benzyl alcohol. Thallium Tl 201 has a half-life of 73.1 hours and is cyclotron-produced. It is essentially carrier-free, and contains less than 0.25% lead Pb 203 and less than 1.9% Thallium Tl 202.

PHYSICAL CHARACTERISTICS

Thallium Tl 201 decays by electron capture to Mercury Hg 201 with a physical half-life of 73.1 hours.[1] Photons that are useful for detection and imaging are listed in Table 1. The lower energy X-rays obtained from the mercury Hg 201 daughter of Tl 201 are recommended for myocardial imaging, because the mean %/disintegration at 68-80.3 keV is much greater than the combination of gamma-4 and gamma-6 mean %/disintegration.

Table 1. Principal Radiation Emission Data

Radiation	Mean %/Disintegration	Mean Energy (keV)
Gamma-4	2.65	135.3
Gamma-6	10.0	167.4
Mercury X-rays	94.5	68-80.3

Martin, M.J. Nuclear Data Project, ORNL, January 1977

EXTERNAL RADIATION

The specific gamma ray constant for Thallium Tl 201 is 4.7R/mCi-hr. at 1 cm. The first half-value layer is 0.23mm of lead. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from the interposition of various thicknesses of lead (Pb) is shown in Table 2. For example, the use of 3.3mm of lead will decrease the external radiation exposure by a factor of about 10,000.

Table 2. Radiation Attenuation By Lead Shielding

mm of Lead (Pb)	Coefficient of Attenuation
0.006	0.5
0.15	10^{-1}
0.98	10^{-2}
2.1	10^{-3}
3.3	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals before and after calibration are shown in Table 3.

Table 3. Thallium Tl 201 Decay Chart: Half life 73.1 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-72	1.98	18	0.84	72	0.51
-60	1.77	24	0.80	78	0.48
-48	1.58	30	0.75	84	0.45
-36	1.41	36	0.71	90	0.43
-12	1.12	42	0.67	96	0.40
-6	1.06	48	0.63	108	0.36
0*	1.00	54	0.60	120	0.32
6	0.95	60	0.57	132	0.29
12	0.89	66	0.54	144	0.26

*Calibration Time

CLINICAL PHARMACOLOGY: Carrier-free Thallous Chloride Tl 201 has been found to accumulate in viable myocardium in a manner analogous to potassium. Experiments employing labeled microspheres in human volunteers have shown that the myocardial distribution of Thallous Chloride Tl 201 correlates well with regional perfusion.

In clinical studies, thallium images have been found to visualize areas of infarction confirmed by electrocardiographic and enzyme changes. Regions of transient myocardial ischemia corresponding to areas perfused by coronary arteries with partial stenoses have been visualized when thallium was administered in conjunction with an exercise stress test. It is usually not possible to differentiate recent from old myocardial infarction, and no exact differentiation can be made between recent myocardial infarction and ischemia.

After intravenous administration, Thallous Chloride Tl 201 clears rapidly from the blood with maximal concentration by normal myocardium occurring at about ten minutes.

INDICATIONS AND USAGE: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction.

It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products – especially those elective in nature – of women of childbearing capability should be performed during the first ten days following the onset of menses.

PRECAUTIONS: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

The expiration date for Thallous Chloride Tl 201 is six days postcalibration.

ADVERSE REACTIONS: Adverse reactions related to use of this agent have not been reported to date.

DOSAGE AND ADMINISTRATION: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

RADIATION DOSIMETRY

The estimated absorbed radiation dose[2] to an average patient (70kg) from an intravenous injection of a maximum dose of 1.5 millicuries of Tl 201 is shown in Table 4.

Table 4. Radiation Dose Estimates of Thallous Chloride Tl 201: Absorbed Dose/1.5mCi Thallium Tl 201 Administered

	Rads/1.5mCi
Heart	0.51
Small Intestines	0.97
Kidneys	2.2
Liver	0.93
Red Marrow	0.51
Ovaries	0.85
Testes	0.81
Thyroid	1.12
Total Body	0.36

[2]Values listed include a maximum correction of 13% to the radiation doses from Tl 201 due to the radiocontaminants Pb 203 and Tl 202

HOW SUPPLIED: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0 and 9.0 millicuries of Thallous Tl 201.

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Introduction

Noninvasive Approaches to Cardiac Imaging: Comparisons and Contrasts

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With the advent of cardiac catheterization and angiographic techniques, substantial advances have been made in the detection of heart disease and in our understanding of its pathophysiology. These advances have resulted in a more precise understanding of coronary, valvular and other forms of heart disease. Although the catheterization approach remains the diagnostic standard in many areas of clinical cardiology, it is expensive and uncomfortable, and continues to have significant, albeit small, morbidity and mortality.

Noninvasive approaches permit cardiac disease to be detected and evaluated with less expense, discomfort and risk than is possible with the catheterization approach. The conventional clinical evaluation of patients with suspected heart disease (the history, physical examination, resting electrocardiogram and chest roentgenogram) remains the initial approach and the prerequisite before considering either noninvasive or invasive testing. However, it is now clear that information can be obtained with noninvasive techniques that cannot be gained either with the conventional clinical evaluation or with cardiac catheterization. In addition, the electrocardiographic stress test and long-term electrocardiographic monitoring, although not discussed herein, constitute important noninvasive techniques that, when used properly, provide information that can obviate the need for the more expensive noninvasive studies or cardiac catheterization and provide data that cannot be obtained by any other approach.

The introduction of a high quality M mode echocardiograph about a decade ago opened up new vistas for noninvasive cardiac study. For the first time valves and ventricular walls could be observed with high resolution using noninvasive, relatively low cost and even portable devices with no apparent risk. This opened the "window" for physicians to obtain anatomic and physiologic information previously available only by cardiac catheterization. In addition, new information about cardiac mechanics, valve integrity and cardiac structure became available. Occult disease could now be identified and new or poorly understood conditions became easily and frequently recognized (mitral valve prolapse and asymmetric septal hypertrophy, for example). However, the major problem with M mode echocardiography was that the perspective provided was limited to an "ice-pick" view of the heart. Innovative advances and technology led to the development of two dimensional echocardiography, a method that allowed tomographic imaging of the heart and therefore more clearly depicted gross cardiac anatomic relations and function.

Important advances in detection and evaluation of heart disease have also been provided by the application of radionuclide cardiac imaging methods that have been refined to permit noninvasive clinical evaluation of myocardial perfusion and integrity and global ventricular function without the geometric assumptions needed in approaches using angiography and ultrasound. Although ultrasonic approaches provide information with high spatial resolution, they suffer from technical interference by bone or lung interposed between the cardiac structures of interest and the echocardiographic probe. In contrast, the radionuclide approaches, while providing information with lower spatial resolution, are virtually unaffected by overlying tissue. The advances in radionuclide methods that led to the evolution of nuclear cardiology included: development

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TABLE I
Noninvasive Cardiac Imaging: Technical Considerations

Method	Approx. Axial Resolution (in mm)	Imaging Ability									Technical Interference From:
		Valve Structure	Valve Motion	Regional Wall Motion	Wall Thickness	Global Vent. Func. (EF)	Chamber Volume & Dimension	Myocardial Blood Flow Pattern	Myocardial Tissue Integrity	In Real Time	
Ultrasound M mode	2	Good	Excellent	Excellent for those areas seen	Excellent	Fair*	Good	None	Fair	Excellent	Bone, lung
2 dimensional	3	Excellent	Good	Excellent	Good	Good	Good	None	Fair	Excellent	Bone, Lung
Radionuclide imaging											
Radionuclide cineangiography†	10	None	None	Good	Poor	Excellent	Fair	None	None	Fair	Marked irregular rhythm
Myocardial imaging (perfusion)	12	None	None	None	Poor	None	Poor	Excellent	Excellent	None	Overlying soft tissue
Infarct avid imaging	10	None	None	None	None	None	None	None	Excellent	None	Bone‡

* Poor, in the presence of abnormal regional wall motion. † First pass or gated techniques. ‡ Using pyrophosphate.
Approx. = approximate; EF = ejection fraction; Vent. Func. = ventricular function.

of new radiopharmaceutical agents such as thallium-201, permitting clinical assessment of myocardial perfusion and integrity, advances in gamma camera technologies permitting higher resolution imaging, application of computer technology to permit acquisition and display of cardiac functional information either through the "first pass" method or the multiframe blood pool imaging approach; and discovery that the bone-imaging agent, technetium-99m–labeled stannous pyrophosphate, accumulated in regions of recently infarcted myocardium. Analogous to ultrasonic imaging, the recent innovative efforts in radionuclide cardiac imaging appear to make it possible to image tomographically in multiple planes as opposed to conventional planar imaging. The advantages of tomographic approaches over conventional planar methods are currently under investigation.

Comparison of echocardiography and radionuclide imaging: Because echocardiography and radionuclide imaging are becoming increasingly available and can be applied to virtually any clinical setting, it seems appropriate to compare these two modalities to define their indications, limitations and comparative values in assessing patients with heart disease in order to optimize clinical utility. Tables I and II compare and contrast the technical aspects and the clinical utility of the two approaches.

The articles in this Symposium describe the current status of echocardiography and cardiac radionuclide imaging as applied clinically. The first two manuscripts address the technical aspects of the ultrasonic and radionuclide methods. These are followed by manuscripts addressing the utility of these modalities in evaluating ventricular function and in the special clinical problem of left ventricular aneurysm. This latter is an example of an entity in which noninvasive techniques have, in many cases, obviated the need for cardiac catheterization.

Valvular heart disease: The next set of manuscripts evaluates the clinical problem of valvular heart disease and points out the important strides made in the recognition of valve abnormalities and their effects on cardiovascular function. For example, two dimensional echocardiography not only has clarified the prevalence of primary mitral valve prolapse syndrome, a condition once thought to be uncommon, but also has replaced left ventricular cineangiography as the diagnostic standard for this important clinical entity.

Coronary heart disease: The detection of coronary heart disease is of major importance in cardiovascular medicine today, and a thorough appraisal of the use of both radionuclide imaging and two dimensional echocardiographic techniques is presented. One example of recent advances is the use of thallium-201 myocardial imaging during stress to enhance the predictive accuracy of exercise testing. In addition, radionuclide cineangiography provides a means of assessing the impact of coronary artery disease on left ventricular function at rest and during exercise. Although these techniques will never obviate the need for coronary arteriography before performing coronary bypass graft surgery, when added to electrocardiographic approaches, they have

TABLE II

Noninvasive Cardiac Imaging: Current Clinical Utility

Detection and Evaluation of Patients With:	Ultrasound		Radionuclide Imaging		
	M Mode	2D	Cineangiography*	Myocardial "Perfusion"	Infarct-Avid
Valve disease	I	I	S	—	—
Intracardiac clots	I	I	S	—	—
Myxoma	I	I	S	—	—
Vegetations	I	I	—	—	—
Stable coronary artery disease	S	S	I	I	—
Acute myocardial infarction	—	S	S	I	I
Myocardial scar	S	S	S	I	S
Ventricular dysfunction (generalized or regional)	S	I	I	—	—
Ventricular aneurysm	S	I	I	S	—
Hypertrophic cardiomyopathy	I	I	S	S	—
Congenital heart disease	I	I	S, (I†)	S	—

* Gated equilibrium or first pass techniques. † Shunt size can be determined by first past method.
I = recommended in the initial evaluation; S = may be relevant after initial evaluation; 2D = two dimensional; — = not recommended.

substantially enhanced the clinical ability to recognize significant coronary heart disease. In addition, the radionuclide imaging techniques have enhanced our clinical ability to detect acute myocardial infarction. The status of radionuclide and ultrasonic methods in the evaluation of the patient with possible or definite myocardial infarction is described.

Cardiomyopathy: New strides made possible by noninvasive techniques in the area of cardiomyopathy are presented in the next pair of manuscripts. For example, the clinical spectrum of hypertrophic cardiomyopathy has been defined by two dimensional echocardiography to provide a highly specific diagnosis without cardiac catheterization. The role of radionuclide imaging techniques in the assessment of cardiomyopathies and in the differential diagnosis of ischemic versus idiopathic congestive cardiomyopathy is discussed.

Congenital heart disease: The recognition and evaluation of adult congenital heart disease has been advanced in recent years by the use of two dimensional echocardiography, which often can demonstrate the actual "defect" in atrial and ventricular septal defects and characterize precisely the great vessel-ventricular relations in cyanotic congenital heart disease. Thus, a rapid and accurate diagnosis in critically ill patients can be made noninvasively. First pass radionuclide techniques can accurately quantify the magnitude of the intracardiac shunt.

New technologies: Noninvasive cardiac testing has grown so rapidly in sophistication that new technical forms of imaging have been developed that in the future may enhance our diagnostic armamentarium. The final four manuscripts in this symposium evaluate the status of new potentially useful technologies for noninvasive evaluation of the heart. Doppler echocardiography can localize and depict abnormal intracardiac flow patterns such as those associated with valve regurgitation. New tomographic imaging approaches for evaluation of cardiac structure, function and metabolism utilize X-rays (transmission tomography), positron-emitting radiotracers (emission tomography) and, most recently, nonionizing magnetic and radio frequency fields (zeugmatography). Table III compares and contrasts these new technologies with those currently available.

Future potential and advances: The future potential of noninvasive cardiac imaging is enormous. We can look to computer technology to enhance storage, display and analysis of ultrasonic studies. Such improvements would allow a more accurate rendition of cardiac structures and provide for three dimensional

TABLE III

Comparisons and Contrasts of Currently Available and Potential New Cardiac Imaging Techniques

Imaging Modality	Biological Hazzard	Resolution (in mm)	Technical Interference	Technical Advantage
Ultrasound				
M mode echocardiography	None known	2	Bone, lung	Rapid intracardiac motion
2D echocardiography	None known	3	Bone, lung	Realtime cardiac structural relations
Doppler	None known	5	Bone, lung	Localization of disturbed flow patterns
Radionuclide imaging				
Gamma approaches	Ionizing radiation	10	Bone, soft tissue	Myocardial perfusion function and tissue integrity
Positron approaches	Ionizing radiation	10	None	Myocardial perfusion and metabolism
X-ray imaging				
Computerized tomography	Ionizing radiation	~1	Bone	Cardiac structural relations, ?coronary anatomy
Nuclear magnetic resonance	None known	~1	None	?Cardiac structure, function & metabolism without tracer administration

ND POHOST

t echocardiography with a variety of
ay an increasing role in the detection
and pressure conditions and lead to
ing of cardiac dynamics. Availability
ogy to provide a high quality pocket-sized
iocardiograph will allow for even more clinical flexibility than is possible with existing portable ultrasonic equipment.

Conventional gamma camera approaches might be improved by advances in computer and gamma camera technology to allow better quantitation of wall motion and myocardial perfusion and viability, and by the development of improved radiopharmaceuticals to permit higher resolution imaging. Positron imaging permits the use of a large array of metabolically active radiopharmaceuticals with a short half-life. The development of radionuclide generators for the production of these short-lived positron-emitting radionuclides might ultimately obviate the need for expensive on-site cyclotrons and, therefore, permit more widespread application of positron imaging. Computerized X-ray tomography may ultimately permit accurate ventricular and coronary angiography with only an intravenous injection of radiopaque contrast medium. Finally, the newest noninvasive approach, nuclear magnetic resonance imaging, using combined magnetic and radiofrequency fields, has enormous potential to obtain not only high resolution structural information, but also in situ metabolic information, probably without the need for tracer administration. Such advances should lead to more accurate detection of cardiac disease and a better understanding of the physiologic, biochemical and pathologic alterations that occur in cardiac disease states. Much work will be needed before the full potential of these noninvasive approaches can be realized.

Cross-Sectional Echocardiography: Physical Principles, Anatomic Planes, Limitations and Pitfalls

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Although M mode echocardiography has achieved a prominent role in the diagnosis and management of patients with cardiovascular disease, the limited area of view afforded by M mode techniques has restricted the application of ultrasound in many areas. The development of two dimensional echocardiography has obviated many of the limitations inherent in the narrow view of the M mode technique. It has enabled imaging of the heart from additional transducer locations, permitted determination of shape and anatomy and provided the ability to determine motion along two axes. Several types of two dimensional echocardiographs have been developed, and each type offers both advantages and disadvantages. Although two dimensional echocardiography has provided a larger area of view with ultrasound, it has also introduced new limitations including a larger and bulkier transducer, a much reduced sampling rate and a difficult display medium (videotape). In addition, new considerations regarding ultrasonic resolution have been raised. Two dimensional techniques have resulted in new pitfalls in ultrasonic diagnosis related to instrument artifacts as well as to performance and interpretation of the examination. The spurious appearance of cardiac masses because of these ultrasonic artifacts represents a particularly prominent diagnostic pitfall that must be avoided in daily practice. It is anticipated that the new wider field of view provided by two dimensional echocardiography combined with a standard high resolution capability of ultrasound (2 to 4 mm) will result in an increasingly large role for echocardiography in the management of patients with heart disease.

The development of M mode ultrasonic techniques enabled the noninvasive evaluation of dynamic intracardiac anatomy for the first time. Soon time-motion recordings became recognized as the diagnostic procedure of choice for many cardiovascular disorders including pericardial effusion,[1] cardiac tumors[2] and asymmetric septal hypertrophy.[3] Unfortunately, M mode echocardiography affords only an "ice-pick view" of the heart, or an image of the heart that is restricted at any given time to the narrow area included within the ultrasonic beam. An analogy has been drawn between probing the heart with an M mode beam and examining a darkened area by means of a flashlight; each technique allows perception of only those objects that fall within the path of the beam at that time. Therefore, although it conveys anatomic information, the M mode echocardiographic recording consists of a series of undulating lines that are more reminiscent of an electrocardiogram than of an angiogram.

The development of two dimensional echocardiography was intended to obviate several of the limitations inherent in the "ice-pick" view of the M mode echocardiogram. The narrow diameter of the M mode beam does not provide spatial orientation, and it is necessary to identify cardiac structures either by their pattern of movement or by their relation to

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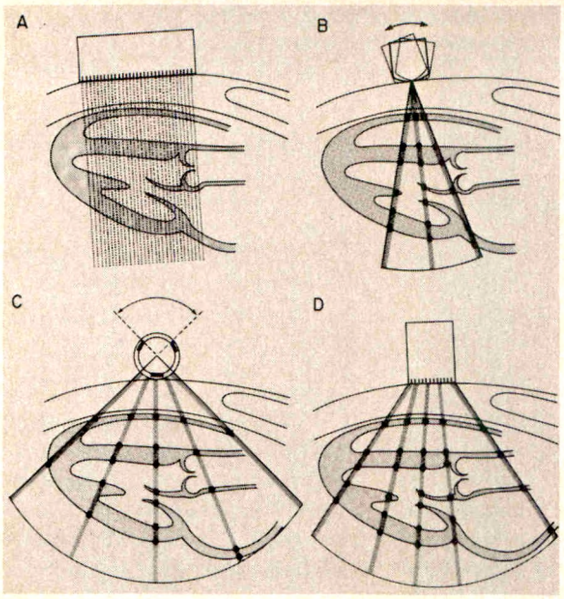


FIGURE 1. Various types of real time two dimensional echocardiographic units. **A**, a linear array transducer; **B**, a narrow angle oscillating mechanical sector scanner; **C**, a 360° rotary mechanical sector scanner; **D**, a phased array device utilizing electronic beam steering.

other landmarks by time-motion techniques. Therefore, the anatomy traversed by the ultrasonic beam can be determined with certainty only from a few standardized points of examination that enable the simultaneous recording of several cardiac structures. Thus, it has been impossible to determine the precise transcardiac plane of the M mode ultrasonic beam with the transducer positioned at the point of maximal cardiac impulse. M mode echocardiography is also incapable of accurately portraying the shape or anatomy of cardiac structures. For example, in the evaluation of aneurysmal dilatation of the aorta, M mode echocardiography is incapable of distinguishing fusiform from sacular aneurysms.[4] Finally, in being limited to a one dimensional projection (usually anteroposterior), M mode echocardiography cannot determine the additional relative position or movement in another direction. Indicative of this limitation was the reported failure of M mode echocardiography to reveal the prominent superior motion that frequently accompanied movement in a posterior direction in mitral valve prolapse.[5]

Cross-sectional echocardiography expanded the size of the ultrasonic beam and thereby provided the simultaneous acquisition of anatomic information in a second dimension. To follow the analogy, one was now dealing with a floodlight rather than a flashlight in examining the heart. The second dimension afforded by cross-sectional techniques provided spatial orientation throughout a large segment of the heart. Therefore, the plane of the examining beam could be known with certainty and echocardiograms could be recorded from additional transducer locations.[6,7] The increased field of view of cross-sectional echocardiography also allowed the delineation of the perimeter of cardiac structures, thereby enabling the determination of shape and anatomy for the first time. Finally, the two dimensional approach enabled the resolution of position or motion that occurred in a second plane (superior-inferior or medial-lateral) to that of the anterior position. Accordingly, cross-sectional echocardiography substantially expanded the diagnostic information available with time-motion techniques.

Cross-Sectional Echocardiographic Techniques

A variety of techniques have been developed to obtain cross-sectional echocardiograms. Each technique reconstructs an image of the heart from several individual discrete B mode ultrasonic scan lines. As might be expected, each technique has advantages and disadvantages, and the perfect cross-sectional echocardiograph has not yet been devised.

B mode reconstruction: One of the earliest attempts to produce two dimensional ultrasonic images of the heart consisted of B mode scanning.[8] Thus, ultrasonic signals from cardiac structures were obtained by a standard M mode echocardiograph whose transducer was attached to a potentiometer capable of indicating orientation in space. The signals obtained were displayed on the vertical axis of the tracing as dots whose depth and brightness were related to their distance from the transducer and to amplitude, respectively. Rather than sweeping these vertical signals along a horizontal axis with time as in M mode echocardiography, multiple scan lines were obtained at various transducer positions and angulations, displayed in a position analogous to their orientation in space and combined to "form" composite cardiac images. To account for the prominent motion exhibited by the heart it was necessary to obtain ultrasonic signals at only a selected period during the cardiac cycle, a process made possible by gating the echocardiograph to the electrocardiogram. Accordingly, multiple cardiac cycles were required to construct a cardiac image, a lengthy procedure that prohibited real time imaging. Further, the electronic circuitry required for spatial orientation restricted free angulation of the ultrasonic transducer.

Linear array: Several technical approaches have been taken toward the development of an echocardiograph capable of providing two dimensional images of the heart in real time (Fig. 1). One of the first units developed that provided real time two dimensional echocardiographic images was the linear array system.[9–11] This system is relatively simple and consists of a row of standard M mode piezoelectric elements each of which emits and receives ultrasonic signals independently to provide a single B mode scan line of data. The composite record obtained from the 30 to 64 individual B mode scan lines available is a rectangular two dimensional image whose size is determined by the size of the transducer (Fig. 1A). The image is compromised by the fact that ultrasonic targets are widely separated because of gaps between the individual elements where no data is recorded. The advantages of the linear array systems are a relatively high frame rate (due to elec

tronic scanning and a small number of scan lines), the ability to produce an M mode recording from any selected area within the field of vision and good resolution in the near field. A disadvantage of these systems is that the transducer is of necessity large and difficult to manipulate into a thoracic window, which avoids the nonultrasound-transmitting ribs and lungs. In addition, there is some problem with cross talk between the individual elements.

Mechanical sector scanners: The next major approach toward obtaining real time cross-sectional images of the heart consisted of the development of mechanical sector scanners.[12,13] The initial mechanical sector scanners utilized a single M mode ultrasonic transducer to obtain all B mode scan lines. The transducer is attached to an electric motor that rapidly steers it through a fixed circular axis with an arch of 30° to 60°. As with B mode scanning, electric potentiometers are affixed to the transducer to determine its orientation in space, and the individual B mode scan lines are depicted in an analogous position on the echographic recording. The net result is a cross-sectional image of the heart composed of a number of radial B mode scan lines presented in a circular sector format of 30° to 60° arc (Fig. 1B). The advantage of such mechanical sector scanners is that they are relatively simple in engineering aspects and enable adaptation of many existing M mode units for cross-sectional capabilities. In addition, the signal to noise ratio of these units is among the highest of any cross-sectional echocardiographs. The line density of these units is substantially higher than that achieved by linear scanners. The disadvantage of the mechanical sector scanner is that the transducer oscillates on the chest wall, thereby limiting the arc through which the ultrasonic transducer can be driven while still maintaining contact with the skin. The net effect is a cross-sectional echocardiograph that is limited in arc, therefore yielding a relatively narrow field of vision of cardiac structures.

In an attempt to create wide angle cross-sectional echographic images by mechanical beam steering, echographs have been developed in which three or four individual ultrasonic piezoelectric elements are rapidly propelled through a 360° circle of rotation by a motorized device (Fig. 1C). Each of the ultrasonic elements provides B mode scan lines through only a segment of its total circular rotation, usually 80° to 90°. To achieve an image the ultrasonic elements have to be removed from contact with the skin, a process achieved by enclosing them in oil within a plastic housing. The net effect of utilizing multiple elements that rapidly rotate in a single direction is to enable a wide angle real time sector scan of the heart to be recorded from a mechanical device. The bulky plastic and oil housing used by rotary scanners to enclose the ultrasonic crystals may result in some degradation of the ultrasonic images by decreasing the target to noise ratio, producing reverberation artifacts from the plastic housing itself, and permitting the formation of air bubbles within the oil medium that interfere with sound propagation. In addition, utilization of multiple transducer elements requires that the piezoelectric crystals be nearly identical in regard to acoustical properties, and a potential for image degradation exists if elements are mismatched.

Phased array: The most recent approach to two dimensional real time cardiac imaging is phased array scanning, which presents both the greatest technical complexity and the greatest potential of the major methods for obtaining such recordings.[14,15] Phased array scanners utilize aspects of both linear array and mechanical sector technology (Fig. 1D). Thus, similar to linear array units, phased array devices utilize multiple ultrasonic elements to send and receive the ultrasonic signal. However, rather than utilizing these elements independently phased array echographs activate all elements in conjunction to obtain a single ultrasonic beam, which is then electronically steered through a circular sector arc with a fixed axis similar to that of mechanical units.

Phased array devices depend on Huygen's principle, which states that multiple small wave fronts of sound will invariably combine to form a single large sound wave whose direction will be determined by the component wavelets. In phased array units the individual ultrasonic elements are sequentially activated with programmed time delays so that a series of distinct small wave fronts are produced that ultimately unite to form a single sound wave. Further, the direction of the resultant sound wave is determined by the relative timing of the individual wavelets; by altering the time delay of element activation the ultrasonic beam can be rapidly oscillated through a sector arc by purely electronic means. The beam may likewise be focused by manipulating the sequence of element pulsing.

Phased array scanners offer many potential advantages for obtaining real time cross-sectional echocardiographic images. Wide angle images of high line density and adequate frame rate are readily obtainable. In addition to the electronic focusing capable of implimentation for the transmitted beam, rapid manipulation of the timing of element activation can also be coordinated by a computer to result in focusing of the ultrasonic signal throughout its range of depth in the receiving mode. Such dynamic focusing can provide excellent resolution in depth as well as in lateral field (Fig. 2). Finally, the lack of motion of the transducer enables one or even more than one M mode recording to be obtained simultaneously with that of the two dimensional image, a potential that may also be extended to simultaneous two dimensional and Doppler ultrasonic recordings (Fig. 3). A disadvantage, of course, is that phased array technology is highly complex and thus far has required the units to be both large and expensive. In addition, the signal to noise ratio has been somewhat low in the dynamically focused units, and ultrasonic artifacts referred to as side lobes peculiar to phased array systems have presented new problems in echocardiographic interpretation. Finally, to achieve electronic focusing, the size of the element array, and thus the transducer, must be large enough that the focal point of the sound beam is within the transition range of the array.

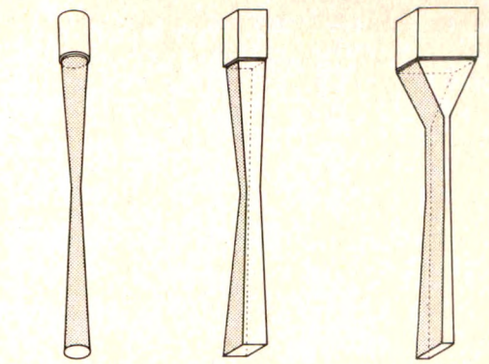


FIGURE 2. Ultrasonic beam profiles for two dimensional echocardiographic units utilizing mechanical beam steering (**left**) and phased array devices utilizing electronic beam steering without dynamic focusing (**center**) and with dynamic focusing (**right**). Note that the single crystal beam is circular in configuration, whereas the phased array beams are rectangular with an expanse of the beam parallel to the width of the transducer as well to the length of the transducer.

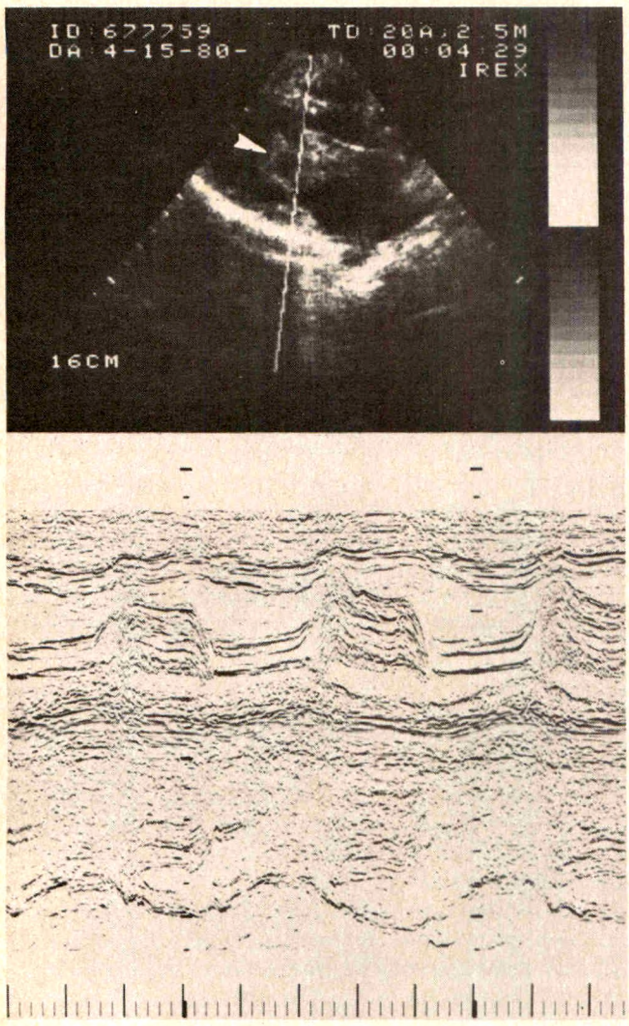


FIGURE 3. Two dimensional (**top**) and M mode (**bottom**) echocardiograms obtained and recorded simultaneously in a patient with a left atrial myxoma (**arrow**). The two dimensional image shows how the tumor movement results in the appearance of a cloud of echoes behind the mitral valve.

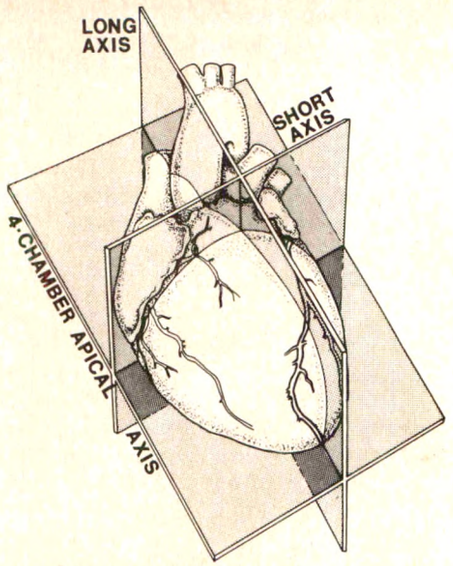


FIGURE 4. The basic three orthogonal planes through which the heart and great vessels may be traversed by a two dimensional sector-shaped ultrasonic beam.

Two Dimensional Echocardiographic Anatomy

Currently, nearly all cross-sectional real time echocardiographic imaging is performed with either mechanical sector scanners or phased array devices. Regardless of which approach is taken a fan-shaped echocardiographic beam ranging from 30° to 90° in arc is available to the examiner and may be directed into the heart through an almost infinite variety of tomographic planes. At present, certain standardized echocardiographic projections have evolved that constitute the basis of most routine examinations[16]; the American Society of Echocardiography has recently made recommendations regarding uniform nomenclature and presentation of these views.[17]

All tomographic views of the heart may be characterized in terms of three orthogonal planes (*Fig. 4*). The long axis plane is that which extends from the aortic valve to the apex of the left ventricle, whereas the short axis plane is that perpendicular to the long axis plane. The four chamber plane is perpendicular to both long and short axes and traverses both the left and right ventricles in a near frontal projection. Cardiac images traversing these planes can be obtained with the transducer positioned along the left parasternal border or at the cardiac apex or in the suprasternal or subcostal locations.

Long axis plane: The conventional long axis view of the heart is obtained with the transducer positioned in the left parasternal area so that the fan of the ultrasonic beam extends from the right shoulder to the left iliac crest, thus traversing a plane from the aortic valve to the apex of the left ventricle. This view represents the arc through which the M mode transducer was moved in traditional M mode echocardiographic scans (Fig. 5, top). By convention, the long axis tomogram is presented with the patient on his back with the head to the right and the legs to the left. The image is displayed as

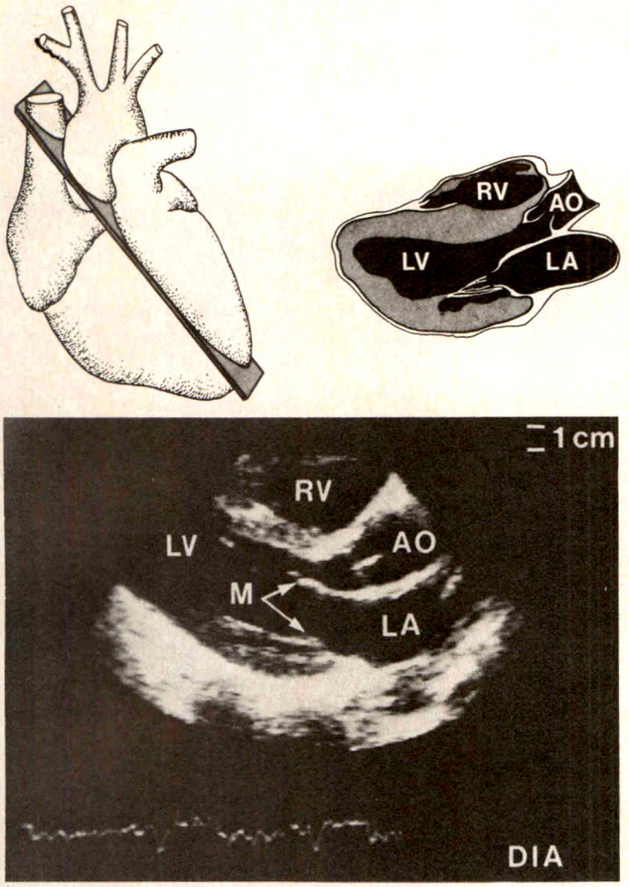


FIGURE 5. Top, long axis plane of a two dimensional echocardiogram (**left**) with a schematic illustration of the cardiovascular structures from which ultrasonic signals are obtained in this plane (**right**). The beam is oriented from the patient's right shoulder to the left iliac crest in this view. **Bottom,** diastolic (DIA) two dimensional echocardiogram obtained in the long axis plane in a normal subject. In diastole the mitral valve leaflets (M) are in the open position (**arrows**) whereas in systole (not shown) the aortic valve leaflets are open and the papillary muscle may be seen. AO = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

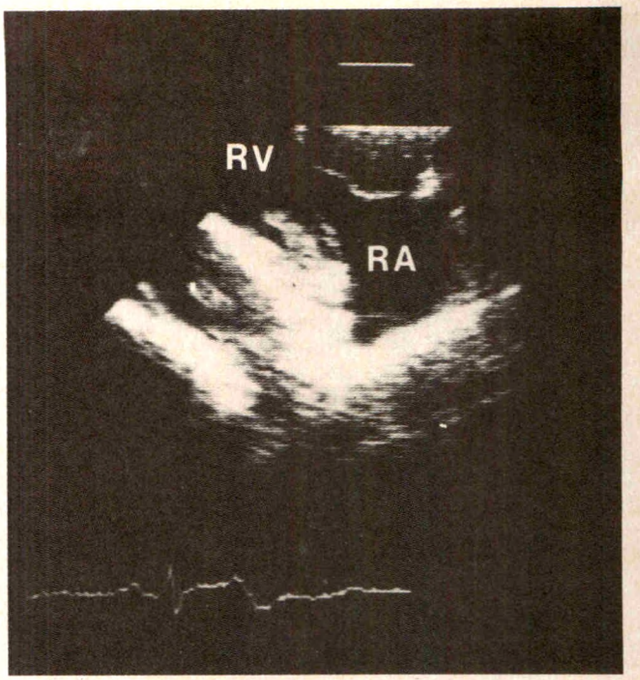


FIGURE 6. Two dimensional echocardiogram recorded from the long axis plane of the right ventricle (RV) obtained from the parasternal position in diastole. RA = right atrium.

if the viewer were standing at the patient's left shoulder so that the right ventricular body and outflow tract are the uppermost structures, with the left ventricle below and to the left, and the aorta and left atrium below and to the right. The aortic valve leaflets, mitral valve leaflets and papillary muscles are often included in this view (Fig. 5, bottom). Obviously, a number of long axis planes parallel to that which traverses the center of the left ventricle may be recorded, and the appearance of the cardiac images will vary depending on the plane obtained. A long axis cut can also be obtained from a transducer positioned at the cardiac apex. Finally, the transducer may be tilted slightly inferiorly and medially to obtain a long axis view of the right ventricle in which the right ventricle, right atrium and tricuspid leaflets may be clearly visualized (Fig. 6).

Short axis plane: With the transducer still in the left parasternal area, the short axis view may be obtained by a 90° rotation from the central long axis so that the wedge-shaped ultrasonic beam traverses the body from the left shoulder to the right iliac crest (Fig. 7). The short axis tomogram is customarily presented as if the viewer were standing at the left iliac crest and looking toward the aorta. Therefore, an ultrasonic tomogram at the level of the mitral valve leaflets would depict the right ventricle as a triangle-shaped structure in the upper portion of the picture while the circular left ventricle would be seen below with the mitral valve leaflets within it (Fig. 8A). Again, the heart may be "bread-loafed" by a number of short axis planes parallel to that obtained through the mitral valve leaflets, and the appearance of the cardiac structures traversed will be dependent on these planes. A short axis view of the left ventricle obtained at the level of the papillary muscles will show the papillary muscles at approximately the 3 and 8 o'clock positions (Fig. 8B). Conversely, if the plane of the ultrasonic beam traverses the base of the heart, the right ventricular outflow tract, aorta and left and right atrium will be visualized (Fig. 9).

Four chamber plane: With the transducer positioned at the point of maximal cardiac impulse, cross-sectional echocardiograms may be obtained with the fan of the ultrasonic beam directed in a fashion similar to either the long axis or short axis orientation. When the ultrasonic beam is positioned in the short axis projection or pointed so as to be directed cranially and slightly posteriorly toward the right scapula with the fan extending from right to left, the so-called four chamber view of the heart will be obtained (Fig. 10). The four chamber view represents a near frontal plane and traverses both ventricles and both atria, as well as both atrioventricular valves. By convention, the four cham-

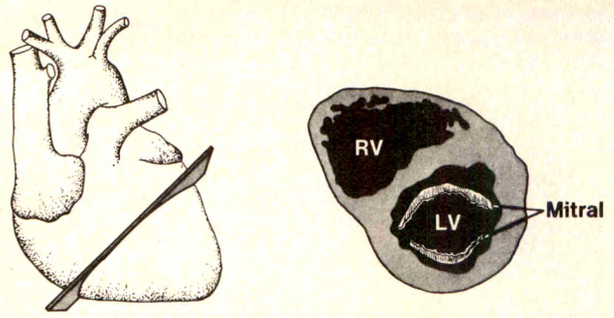


FIGURE 7. Short axis plane (**left**) in which the ultrasonic beam is oriented from the patient's left shoulder to right iliac crest. A schematic illustration (**right**) of the cardiovascular structures recorded at the level of the mitral valve leaflets in this plane. Abbreviations as before.

ber view is most often presented as if the heart were hung from the top of the display screen from the apex (Fig. 11). Accordingly, the cardiac apex is exhibited at the top and the atria at the bottom of the image, and the interventricular and interatrial septa serve to bisect the heart vertically into right-sided chambers on the left and left-sided chambers on the right. The ultrasonic signals from the mid and superior portions of the interatrial septum frequently drop out in this projection, leading to incomplete visualization of this structure. Typically, portions of both the mitral and tricuspid valve leaflets may be simultaneously recorded in this view. Multiple additional tomograms parallel to the four chamber and long axis planes may be obtained from the cardiac apex, and the transducer may also be manipulated through a 360° rotation about the long axis from the thoracic window.

Two chamber apical plane: With the transducer at the cardiac apex in the four chamber position, counterclockwise rotation will bring the ultrasonic beam int the standard long axis orientation. Slight clockwise o lateral angulation, or both, of the transducer from thi long axis plane so that the ultrasonic beam is nearl parallel to the septum will yield the two chamber apica view consisting of the left ventricle and the atrium (Fig 12). In the two chamber view, segments of the antero lateral and inferior walls of the left ventricle are re corded analogous to those imaged in the standard righ anterior oblique cineangiogram.

Subcostal or subxiphoid views: The transduce may also be positioned in the subcostal or subxiphoi area of the abdomen to obtain cross-sectional echocar diographic images. With the transducer in the long axi projection in the subcostal region, a view similar to th apical four chamber view may be obtained, a view par ticularly valuable for visualizing the entire interatria septum (Fig. 13). The short axis orientation of th transducer will yield images similar to those seen in th parasternal area when directed at the level of the ven tricles, although such images will be altered in rotatior Of particular value from the subcostal area is a vie obtained with the fan through a modified short axis typ of orientation at the level of the base of the heart so a to image the right ventricle, pulmonary artery an pulmonary valve leaflets (Fig. 14).

Suprasternal views: The last major location fror which cross-sectional echocardiographic images c clinical value are obtained is the area of the suprasterna notch. The most clinically useful view obtained from th suprasternal notch is that obtained when the ultrasoni beam is directed parallel to the course of the aortic arch By convention, cross-sectional echocardiograms ob tained from the suprasternal notch in this manner de pict the ascending aorta to the left with the descendin aorta to the right, with great vessels imaged superiorl

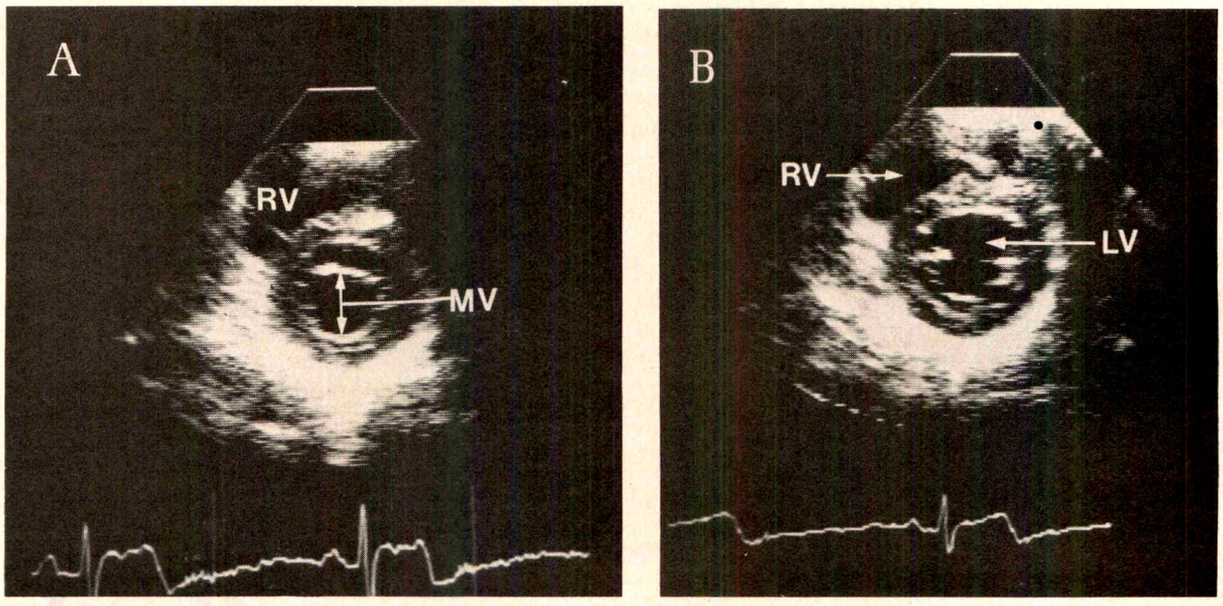


FIGURE 8. Representative short axis two dimensional echocardiograms obtained at the level of the mitral valve leaflets (MV) (**A**) and papillary muscle (**B**). Abbreviations as before.

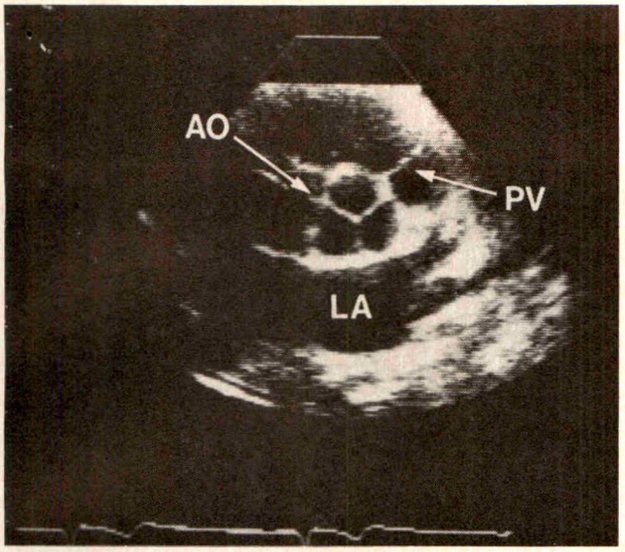


FIGURE 9. Normal two dimensional echocardiogram obtained in the short axis orientation at the level of the aortic valve (AO) leaflets in diastole. PV = pulmonary valve.

and the left atrium and right pulmonary artery seen inferiorly (Fig. 15).

Limitations of Two Dimensional Echocardiography

The ability to obtain wide angle real time two dimensional images of the heart has not been accomplished without the introduction of new technical problems. Thus, in comparison with M mode ultrasonic techniques, a number of compromises have been required in sampling rate and image quality to achieve cross-sectional information. These compromises are important in understanding the limitations of two dimensional echocardiography, and are strong evidence that M mode echocardiographic techniques will not be completely eliminated by, but rather will be complementary to, cross-sectional techniques.

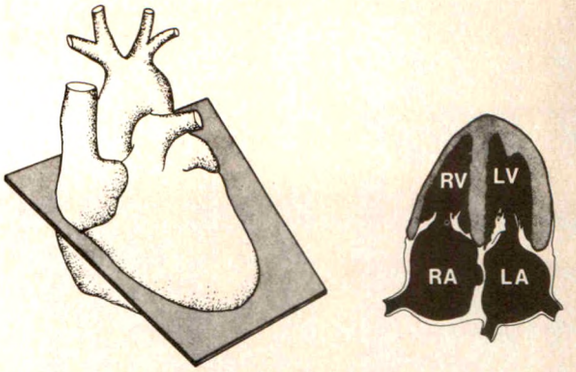


FIGURE 10. Four chamber apical plane obtained with the transducer at the point of maximal cardiac impulse (**left**) and a schematic illustration of the manner in which the cardiovascular structures recorded in this plane are presented during real time recording (**right**). Abbreviations as before.

Transducer design: Two dimensional echocardiography has thus far required disadvantageous alterations in the size and configuration of ultrasonic transducers. A transducer size that is as small as possible is desirable to allow manipulation within the intercostal spaces so as to avoid the ultrasonic barriers of bone and air in the thorax. All currently developed cross-sectional echocardiographic units utilize transducers that are substantially larger than those used in M mode units and that require a larger contact area on the skin. The size of the aperture in the transducers has

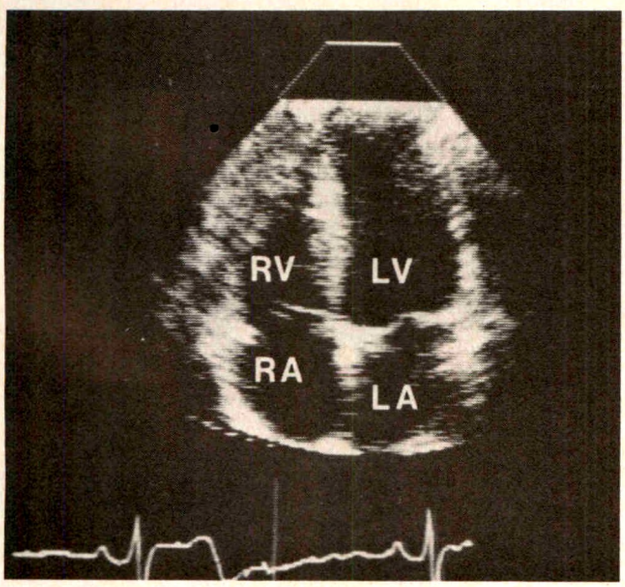


FIGURE 11. Four chamber apical view of a two dimensional echocardiogram. Both mitral and tricuspid valve leaflets may be seen. Abbreviations as before.

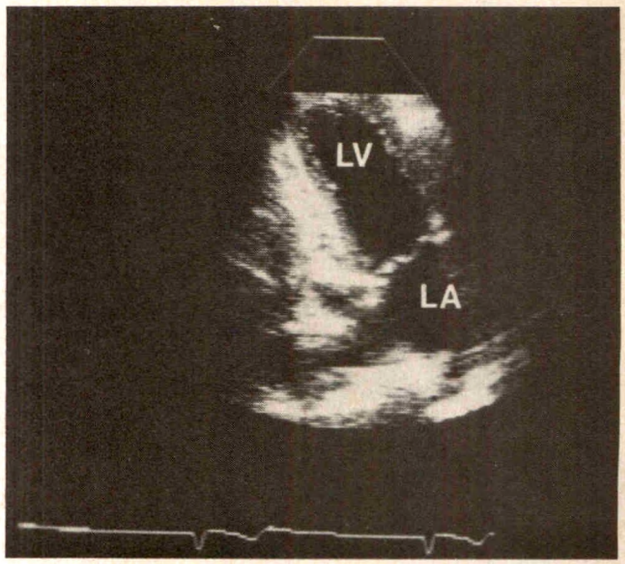


FIGURE 12. Two dimensional echocardiogram obtained from the point of maximal cardiac impulse with the transducer rotated about the longitudinal axis of the left ventricle so as to record the left ventricle (LV) and atrium (LA).

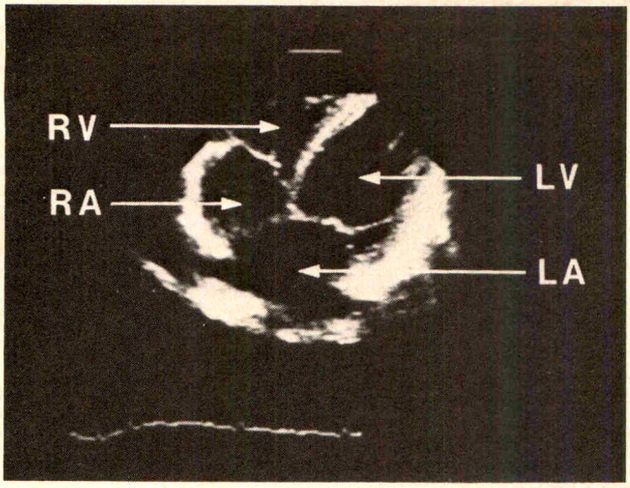


FIGURE 13. Long axis view obtained from the subcostal transducer position. Abbreviations as before.

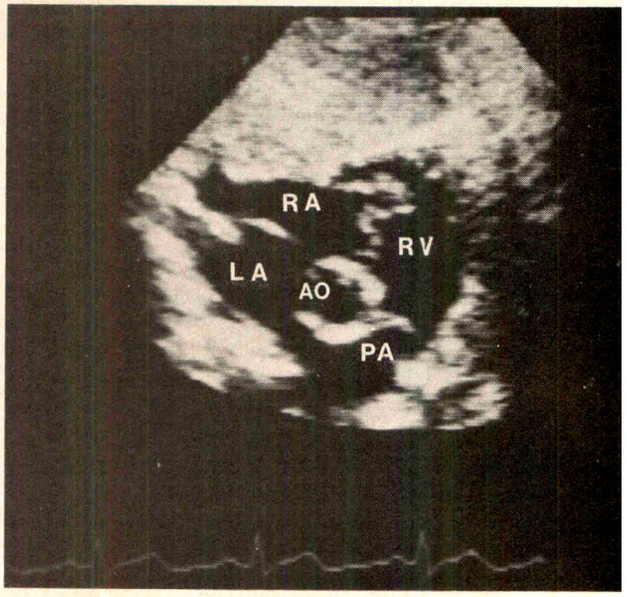


FIGURE 14. View obtained with the transducer angled along the right ventricular outflow tract from a position in the subcostal area. Abbreviations as before.

varied for individual two dimensional units, the largest being present in devices utilizing phase array techniques with dynamic focusing. In addition, mechanical sector scanners have introduced a variety of additional transducer compromises, including moving parts on the chest wall in some units, plastic housing between the transducer and the skin in other units, and unwieldy size and configuration due to interfacing of the piezoelectric crystal with a mechanical rotator. The end result of the alternations in transducer size and configuration has been to limit the ability of the operator to seek small noise-free ultrasonic windows on the thorax through which cross-sectional echocardiograms could be obtained. Occasionally this limitation has made it nearly impossible to obtain some views of the heart, such as the two chamber view from the cardiac apex, and in all cases the larger transducers have provided a barrier for recording ultrasonic images in patients.

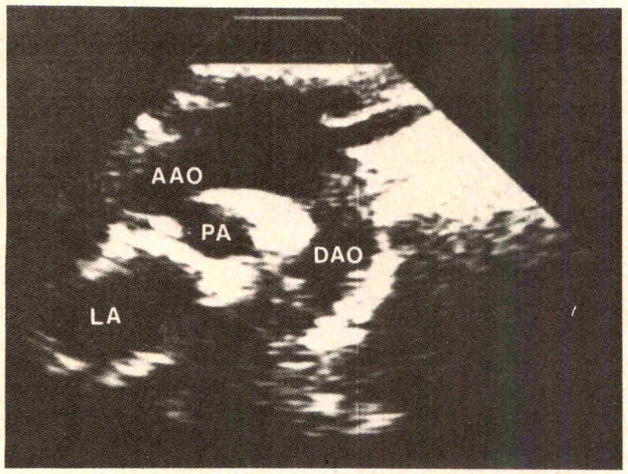


FIGURE 15. Cross-sectional echocardiogram obtained with the transducer positioned in the suprasternal notch and the beam directed parallel to the arch of the aorta. AAO = ascending aorta; DAO = descending aorta; LA = left atrium; PA = right pulmonary artery.

Sampling rate: A prominent limitation of cross-sectional echocardiographic techniques has been the reduced sampling rate available to these units. Compared with M mode echocardiography, which utilizes sampling rates of 1,000 impulses/s, two dimensional echocardiography utilizes sampling rates of 30 to 60 frames/s. Accordingly, although M mode echocardiography is able to delineate continuously the most rapid intracardiac movements, events such as valve opening and closure or fluttering often cannot be accurately depicted with two dimensional techniques, and subtle abnormalities of ventricular wall motion may also be obscured. As is true for other characteristics of echocardiographic performance, the sampling rate varies from unit to unit and may also be dependent on the echocardiographic depth setting utilized.

Display format: The display format now utilized for two dimensional echocardiography is cumbersome and imposes further limitations on this technique. Currently, cross-sectional echocardiograms are displayed directly on an oscilloscope and the images are recorded onto videotape by way of a standard television camera or by means of digital scan conversion for a permanent record and subsequent analysis. With either method the signal processing onto videotape can adversely affect image quality. More important, when one views a stop frame image of the echocardiogram the pattern of motion is lost as an adjunct to identifying targets; only half of the scan lines displayed in real time are exhibited, and the echocardiogram is depicted for only a single interval in the cardiac cycle. Although technical advances may be expected to improve the display formats currently available, two dimensional echocardiography inherently lacks the capacity for simultaneous evaluation of cardiac

motion throughout the cardiac cycle that is currently provided by M mode techniques.

Resolution: The development of two dimensional echocardiography has been accompanied by new considerations and, in some cases, limitations with regard to the resolution of an ultrasonic image. For example, resolution in the near field (the first several centimeters of the image) has been degraded by cross-sectional echocardiographic units. Cross-sectional echocardiography has provided another dimension to the ultrasonic beam that may influence the ultimate resolution of the image. Thus, the ultrasonic beam produced by a conventional single crystal ultrasonic transducer utilized either on M mode or mechanical sector scanner units is circular. Accordingly, the M mode beam may be thought of as having resolution in depth (the axial plane) and in a lateral direction represented as the diameter of the circle (Fig. 2). In contrast, the phased array cross-sectional echocardiographs have an ultrasonic beam with a rectangular configuration, thereby presenting an axial plane and two lateral planes (one parallel to the length and one parallel to the width of the face of the ultrasonic transducer). Thus, resolution in phased array two dimensional echocardiographs may be compromised in the axial plane or in either of the lateral planes.

Axial resolution is similar in mechanical and in phased array echographs and is extremely precise (in the range of 1 to 2 mm). In addition, electronic focusing has been achieved in the axis parallel to the length of the transducer in the transmitting mode in all phased array units, whereas dynamic focusing in the receiving mode has further refined resolution in this axis in some echocardiographs. Lateral resolution in the axis parallel to the length of the transducer has been reported to be approximately 2 mm in dynamically focused phased array devices and 4 to 6 mm in phased array units without this feature. Unfortunately, little attention has thus far been directed to resolution in the axis parallel to the width of the transducer. Lateral resolution is, of course, dependent on the distance of the targets from the ultrasonic transducer as well as on the level of gain utilized for the ultrasonic beam. At present, resolution in the lateral fields constitutes a major consideration in the development and application of two dimensional echocardiography, and is a characteristic that has been degraded in some instruments that are currently available. However, resolution of targets continues to be superior by ultrasound than by other noninvasive cardiac imaging techniques.

Inability to encompass routinely entire left ventricular endocardium: A final point is worthy of consideration in regard to the physical limitations of two dimensional echocardiography. As with M mode echocardiography, two dimensional techniques depend on the reflection of ultrasonic energy from cardiac interfaces that are relatively perpendicular to the ultrasonic beam. Although it is clearly not necessary for a structure to be absolutely perpendicular to this beam in order to reflect sufficient ultrasonic energy to be recorded in an echocardiogram, the more parallel a surface is to the plane of the transducer the less likely it is that a recognizable signal will be obtained. At present, two dimensional echocardiographs do not afford an ultrasonic beam of sufficiently large arc to encompass the entire left ventricle routinely from a point perpendicular to this chamber's long axis along the left sternal border. Although the entire perimeter of the left ventricle may be encompassed by the ultrasonic beam when the transducer is positioned at the cardiac apex and directed parallel to the endocardium of the long axis of the left ventricle, such images often involve significant dropout of the ultrasonic signals from areas of left ventricular endocardium. The difficulty in continuously defining the endocardial perimeter of the left ventricle with two dimensional echocardiography has presented a significant limitation in the evaluation of the left ventricular size and contractile pattern. Further, as would be expected the greater the impediment to ultrasonic transmission within a patient the greater the difficulty in discerning endocardial anatomy with cross-sectional echocardiography.

Ultrasonic Artifacts: Distinction From Cardiac Masses

The appearance of an accumulation or group of echocardiographic signals within the heart during ultrasonic examination is evidence of a cardiac mass. Many cardiac abnormalities may account for the appearance of a cardiac mass on two dimensional echocardiography, including tumor, clot, vegetation, calcification, fibrosis and myxomatous degeneration. Two dimensional echocardiography has provided enhanced ability to identify cardiac myxomas by ultrasound, especially those tumors that are sessile or located in the right-sided cardiac chambers. It has also enabled the recognition of intracardiac thrombi, particularly those in the left ventricle after acute myocardial infarction.[18] In addition, it has aided in the detection of vegetations in patients with infective endocarditis, particularly when the right-sided cardiac valves or prosthetic devices have been involved. Accordingly, two dimensional echocardiography has become the diagnostic method of choice for the recognition of cardiac masses.

Artifacts simulating cardiac mass lesions: Unfortunately, several pitfalls unique to two dimensional echocardiography related to instrument artifacts as well as to performance and interpretation of the examination may lead to the erroneous diagnosis of a cardiac mass. Thus, the use of excessive gain settings of the echograph may lead to the production of echoes from blood within the cardiac chambers that can be mistaken for an intracavitary mass (Fig. 16). This problem appears to be accentuated by two dimensional as opposed to M mode echocardiography, perhaps because of the lesser signal to noise ratio; this emphasizes the necessity to maintain ultrasonic gain settings at the lowest level necessary to obtain good recordings. In addition, two dimensional echographs that utilize phased array technology may produce artifacts that have been called side lobes (Fig. 17). Although the exact cause of side lobes is not known, it is believed that these artifacts are the produce of sound energy adjacent to the main ultrasonic beam related to the gaps between the individual elements in a phased array transducer. These parallel ultrasonic en-

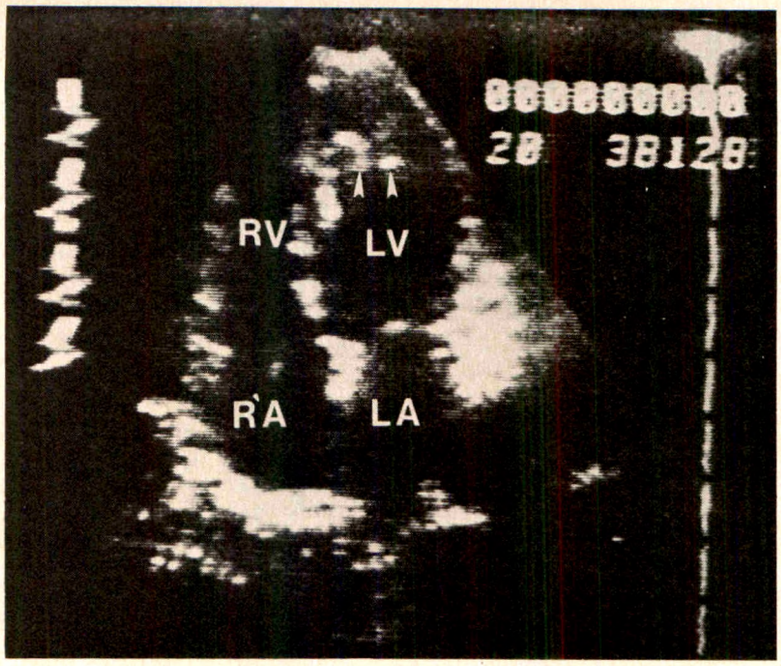


FIGURE 16. Four chamber view of a two dimensional echocardiogram obtained in a normal subject in whom excessive gain settings resulted in the appearance of ultrasonic signals within the apex of the left ventricle (**arrows**). Abbreviations as before.

ergy emissions are capable of producing ultrasonic signals from structures outside the main interrogating beam and may result in the appearance of cardiac structures in positions other than their actual locations. Characteristically, side lobes produce extended echoes from prominent cardiac targets (such as calcium accumulations), which are portrayed as being present throughout the full arc of the sector scan. A relatively unique artifact has been observed with a specific echograph that utilizes a multielement rotary mechanical transducer. This artifact, designated "HERBIE," has been attributed to reverberations from the oil and plastic housing surrounding the ultrasonic elements. It usually appears as a linear rapidly oscillating signal that is predominantly confined to the near field in two dimensional echocardiograms and can often be eliminated by alternate depth settings (Fig. 18).

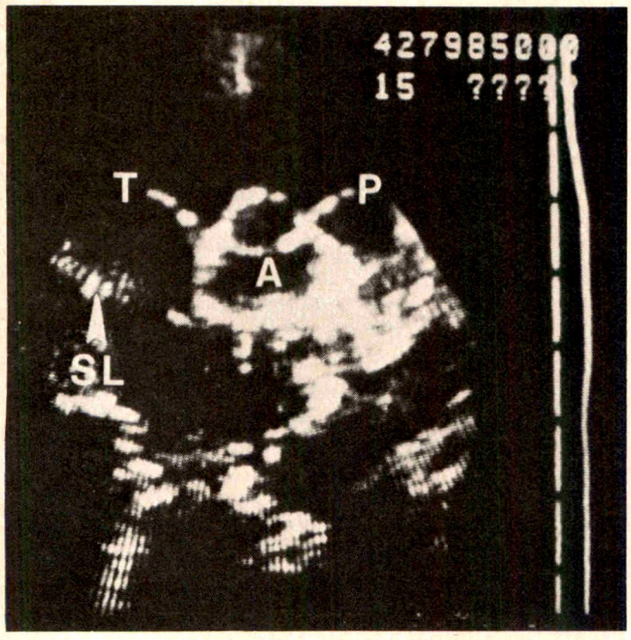


FIGURE 17. Short axis view at the level of the aortic valve leaflets (A) obtained in a patient with prominent side lobes (SL) extending into the area of the right atrium. P = pulmonary valve; T = tricuspid valve.

Anatomic simulators of a cardiac mass: Various anatomic considerations can also influence the spurious appearance of a cardiac mass on two dimensional echocardiography. Thus, prominent trabeculae within the left ventricular cavity may occasionally yield the appearance of a cardiac mass (Fig. 19), particularly simulating a mural thrombus. On occasion, prominent papillary muscles may be mistaken for an abnormal left ventricular mass, especially when only one papillary muscle is within the ultrasonic beam or when unusual tomographic planes are utilized to image the ventricle. Finally, normal structures that are infrequently recorded (such as the Eustachian valve) or structures that are viewed in unusual relation to valves and myocardium (such as chordae tendineae) may be mistaken for intracavitary masses. Again, the echocardiographer must be aware of these possibilities when interpreting a two dimensional echocardiogram.

Differentiation of artifacts from cardiac tumors: At our institution we have found certain rules to be of great value in distinguishing cardiac masses from artifacts. Thus, it has been our experience that nearly all true pathologic masses exhibit some motion throughout

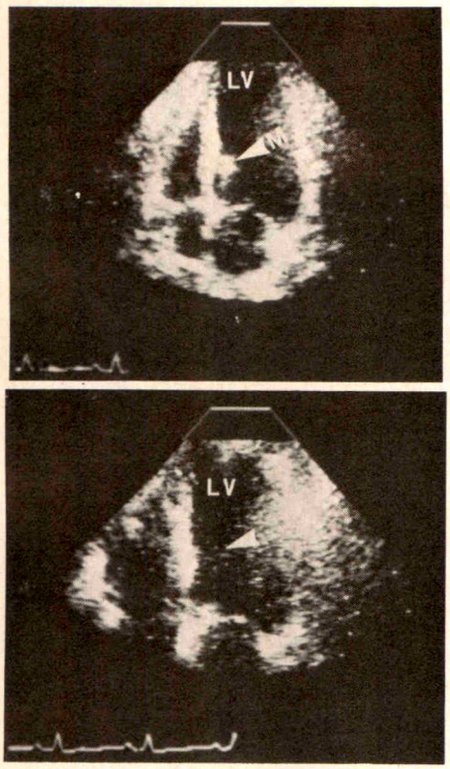


FIGURE 18. Four chamber view of an echocardiogram from a patient without evidence of cardiac disease. An ultrasonic artifact (M) is visualized in the left ventricle along the interventricular septum (**arrow**) (**top**), but is abolished by altering the depth settings of the echocardiograph (**bottom**). LV = left ventricle.

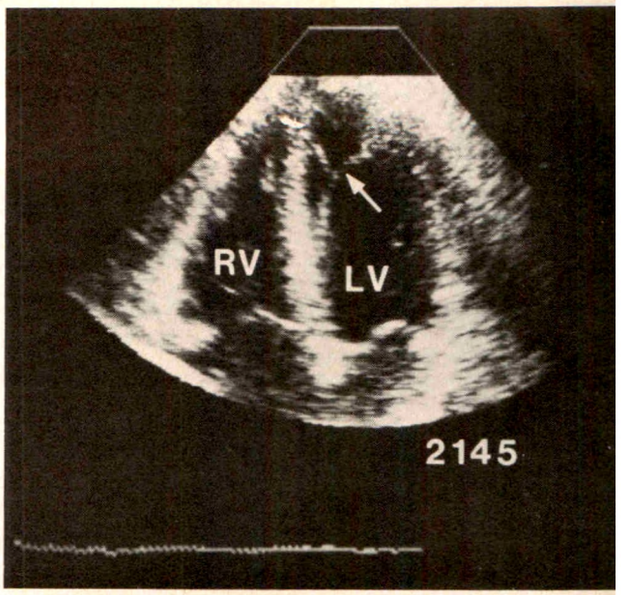


FIGURE 19. Apical four chamber two dimensional echocardiogram demonstrating prominent trabeculae of the left ventricle in the region of the cardiac apex (**arrow**). Abbreviations as before.

the cardiac cycle, be it independent or in conjunction with that of a cardiac structure. The absence of any motion whatsoever is strong evidence that a conglomeration of echoes represents an artifact. Second, nearly all pathologic masses have manifested a defined border that was relatively well circumscribed. Again, the inability to define the borders of the conglomeration of echoes is evidence that the accumulation is artifactual. Because all intracavitary masses without any surface attachment to a cardiac structure would soon be expelled from the heart, the inability to demonstrate such a surface attachment is again evidence that one is not dealing with a true mass. Characteristically, one should be able to visualize a true pathologic lesion in multiple projections of the same anatomic area of the two dimensional echocardiogram. Finally, in our experience all thrombi that have occurred within the left ventricle secondary to acute myocardial infarction or cardiomyopathy have been accompanied by wall motion abnormalities. Therefore, one should be extremely hesitant to diagnose the presence of a cardiac clot in the absence of an abnormal ventricular contractile pattern. We have found that with sufficient experience it has been rare for us to encounter a patient in whom we could not distinguish with confidence a cardiac mass from an ultrasonic artifact.

Conclusion

The ability to examine a wide area of the heart in real time with two dimensional echocardiography represents a significant advance in the diagnosis and management of cardiac disease by ultrasound. Research and development into the technology of two dimensional echocardiography continue, and at present there are advantages and disadvantages to both mechanical and phased array real time cardiac echographs. It is to be anticipated that with future experience two dimensional echocardiography will play an increasingly large role in the management of patients with heart disease.

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Cardiac Nuclear Imaging: Principles, Instrumentation and Pitfalls

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The requirements for cardiac imaging with nuclear techniques are: (1) a radiolabeled tracer that is distributed in proportion to the function under investigation; (2) a collimator to allow photons arising only from specific areas of the heart to interact with the imaging device; (3) an imaging device to convert the gamma photon energy into an electrical signal that can be processed and displayed; and (4) a computer to record the information and permit quantification and optimal display of the data. One characteristic of nuclear imaging techniques is the requirement of averaging of a number of cardiac cycles to provide data for interpretation, whereas the information recorded with nuclear probes can be analyzed on a beat by beat basis. The data can be reviewed both visually and quantitatively. Semiautomatic methods of measuring ejection fraction, which correlate well with data from cardiac catheterization, have been in clinical use for several years. However, these techniques are not capable of correctly analyzing the data from all patients. Particular errors occur with gating, tracking the edge of the ventricle or in the selection of a background area, which may result in the calculation of an erroneous ejection fraction. In the future, short-lived radiopharmaceutical agents will result in a lower radiation burden to patients and higher quality studies in a shorter period of time, and tomographic techniques should provide new insights into the structure and function of the heart.

To measure cardiac structure or function with radionuclides, four phenomena must occur[1,2]: (1) The radiotracer must distribute in the heart in proportion to the function under investigation; (2) the nucleus of the radiolabel must undergo rearrangement to a more stable state with emission of a photon with sufficient energy to traverse the chest wall; (3) the path of the photon must allow it to pass through a hole in the collimator; and finally, (4) the photon must interact in a radiation detector to produce a signal that permits localization of this interaction (Fig. 1). These processes are quite different from those required to perform an ultrasonic examination. Some of the photon energy from the nuclear examination is deposited in the tissues of the patient resulting in a radiation burden from the examination. Even with "worst case" estimates, the burden to the organs receiving the largest dose of radiation is less than 2 rads and less than 1 rad to the whole body. Radiation doses in this range have been used for medical diagnosis for the past 50 years, with no identifiable ill effects. It is reasonable to expect a marked reduction in radiation burden with the development of new short-lived gamma emitting radiopharmaceuticals such as iridium-191 (half-life 4.9 seconds)[3] and krypton-81m (half-life 13 seconds).[4]

The Radiopharmaceutical

Desirable properties of a radiopharmaceutical for cardiac imaging include: (1) localization in the heart in direct proportion to the function under investigation and minimal localization in adjacent structures; (2) release of only gamma photons or X-rays, all with energy sufficient to traverse overlying tissues with no accompanying particulate radiation;

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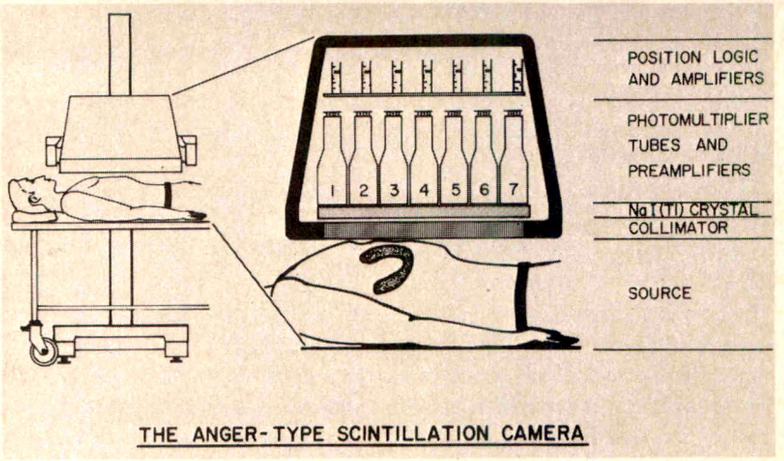


FIGURE 1. Diagrammatic representation of the recording of cardiovascular nuclear medicine data. The patient has received a radiotracer that localizes in the myocardium (**shaded area** in the patient's chest). Photons resulting from the decay of the radiotracer pass through the collimator (**parallel lines** in the radiation detector), and enter the sodium iodide crystal where the photon interacts to cause a flash of light. This light flash is detected by the photomultiplier tubes and is transmitted to the scintillation camera electronics where the location of the interaction with the sodium iodide crystal is determined. The processed signal is sent to a computer system where it is stored and displayed on a screen. When the signals from a series of these interactions have been processed and displayed, the information forms the nuclear image. NaI = sodium iodide; Tl = thallium.

and (3) a half-life sufficient to permit the measurement to be made but to decay at a rate that minimizes the radiation burden to the patient. There are no radiopharmaceuticals available for cardiac imaging at present that meet all these criteria.

Radiopharmaceuticals usually consist of two components: (1) the radioactive portion, the number and type of emissions produced being determined by which radionuclide is used, and (2) the pharmaceutical, which determines the biodistribution of the compound. Radioactive decay results in the rearrangement of the nuclear components of an unstable (excited) atom to a more stable condition and is associated with the release of energy. Because only those results of nuclear rearrangement that can be detected externally are useful for cardiac imaging, only nuclides that primarily emit gamma radiation or X-ray (photons) are commonly used in patient-imaging studies. The concentration of the radiopharmaceutical in the heart provides the information about the function to be measured. Although occasionally a radionuclide can be administered in ionic form to provide the desired functional information, usually the radionuclide with the desired physical properties is chemically bound to a pharmaceutical that determines the biodistribution. Such cardiac radiopharmaceuticals include technetium-99m–labeled pyrophosphate[5,6] for evaluating calcium metabolism; radiolabeled antimyosin to detect destruction of the myocardial cell membrane and identify acutely necrotic zones of myocardium[7]; and carbon-11–labeled palmitic acid to evaluate regional myocardial metabolism.[8]

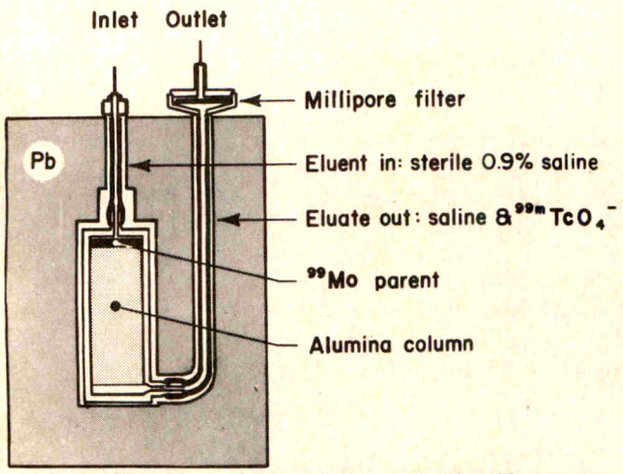


FIGURE 2. Diagrammatic representation of a technetium-99m generator showing the route by which saline solution is passed over the molybdenum-99 (^{99}Mo) parent which is absorbed on the alumina column to produce a sterile eluate of sodium pertechnetate. Pb = lead shielding; TcO_4 = pertechnetate ion.

Technetium-99m: The radionuclides most commonly used in nuclear cardiology are technetium-99m and thallium-201. Technetium, atomic number 43, the first artificially produced element, was made by neutron bombardment of a molybdenum plate in the Berkeley cyclotron by Perrier and Segre[9] in 1937. However, it was not until 1960 that a practical generator system to separate technetium-99m from the molybdenum-99m parent was first described by Richards.[10,11] The generator consists of an alumina column onto which molybdenum-99 (the radioactive parent) is adsorbed and as the molybdenum-99 decays, technetium-99m (the daughter) can be "eluted" by the passage of saline solution (Fig. 2).

Technetium-99m has physical properties that are desirable for clinical use: a half-life of 6 hours, physical decay primarily emitting a single photon of 140 keV with an abundance of 85 photons for 100 nuclear rearrangements, and the convenient generator with a half-life of 67 hours.[12]

Technetium-99m is used in cardiovascular nuclear medicine primarily for infarct and blood pool imaging. Acute infarct imaging is accomplished by chemical binding of technetium-99m to pyrophosphate. The radiopharmaceutical appears to parallel the entry of calcium into damaged cells,[13] a curious phenomenon that occurs even though technetium-99m pyrophosphate is a larger molecule than calcium and probably has an overall charge that is far lower than that of calcium ion. Biologically, technetium-99m pyrophosphate and calcium have only a limited range of similarities, but this

does not detract from the clinical value of the procedure.

The radiopharmaceutical used for blood pool imaging is technetium-99m bound to red blood cells. This may be accomplished by the intravenous injection of stannous ion, usually in the form of stannous pyrophosphate, which appears to change the red blood cell membrane to permit the binding to erythrocytes of subsequently injected technetium-99m.[14] The binding between the technetium-99m and the red cell seems to require a short interval to gain stability. During initial circulation, about 40 percent of the technetium-99m can be removed from the red cells, but after 5 minutes, less than 2 percent of the technetium-99m can be removed from the cells (Leppo, Callahan, Chung, et al., unpublished observations).

Thallium-201: Thallium was discovered by Crookes in 1861. In 1970 Kawana et al.[15] suggested thallium-199 as an agent for imaging the heart. However, it was not until Lebowitz et al.[16] developed a novel method for manufacturing thallium-201 that the potential of this myocardial imaging agent could be realized. The method used to produce thallium-201 involves conversion of stable thallium-203 to lead-201 by bombardment in a cyclotron, with subsequent decay to thallium-201.

Thallium-201, although widely used for imaging, has two unfavorable physical properties: (1) a half-life of 73 hours, which is much longer than that required for clinical measurements; Wagner and Emmons[17] suggest that the appropriate effective half-life of a radiopharmaceutical for metabolic determinations should be 0.693 × the interval of the measurement. A half-life of only 2.7 hours would therefore be required for myocardial perfusion and redistribution measurements (assuming a 4 hour interval between the initial injection at maximal stress and delayed imaging). Studies[18,19] on the whole body distribution and retention of thallium-201 have determined that the biologic half-life of thallium-201 is 10 days. Thus, the effective half-life of thallium-201 in the body approaches the physical half-life, which results in exposure to radiation long after the desired measurements have been completed. (2) The emissions of thallium-201, primarily the 69 to 80 keV mercury K X-ray resulting from the decay of thallium-201 to mercury by electron capture, are less energetic than the gamma photons from technetium-99m, and therefore have a higher likelihood of absorption or scatter within the body, thus limiting the quality of a cardiac image that can be recorded with this radiopharmaceutical.

Thallium-201 is useful for myocardial imaging because, as with radiopotassium, there is a linear relation between thallium-201 deposition and regional blood flow in the myocardium, kidney and skeletal muscle.[20] Although the initial concentration of thallium and potassium in the myocardial cell appears to occur through mechanisms that are related to cardiac output, the rate of loss of these ions from the cell under both normal and ischemic circumstances indicates that the two substances behave very differently.[21,22] However, this difference in biologic behavior between thallium-201 and potassium does not alter the diagnostic value of thallium-201.

The Imaging Device

Camera: The scintillation camera is the standard device in nuclear medicine for imaging the heart. This instrument is equally sensitive to radiation across its field of view and is capable of localizing the relative position of a gamma photon interaction in the sodium iodide crystal of the detector. There are two common types of scintillation camera: single crystal[23] and multicrystal.[24] The *single crystal device* uses a positioning technique evolved by Anger: When a gamma photon interacts with the sodium iodide crystal it causes a flash of light (scintillation) to occur. The scintillation is brightest at the site of interaction but, because the crystal is clear, the light is propagated throughout the entire crystal. An array of photomultiplier tubes views the crystal, and each phototube detects some fraction of the light output of the event. By comparing the intensity of light observed by each tube, the location of the gamma interaction producing the scintillation can be determined.

The multicrystal camera uses an array of discrete sodium iodide crystals that are viewed by a bank of photomultiplier tubes where each crystal causes a signal to appear in the unique arrangement of phototubes. This array approach has the advantages of high speed processing and a higher count rate capability than the Anger camera. However, the Anger camera has the capacity for higher resolution than the multicrystal detector which, intrinsically, cannot resolve anything smaller than the size of a single crystal element (usually 1 cm^2).

Collimator: In the generation of an image, only those photons arising from areas perpendicular or at some known angle to the crystal should be allowed to reach the detector. Because there is no method available to "focus" gamma rays, it is common practice to screen out stray photons from other areas by collimation. Only a very small fraction of photons arising from a radiopharmaceutical in the heart succeed in passing through the chest wall, through the collimator and into the detector. Collimators are designed with regard to both resolution and sensitivity.[25] The primary difference in resolution between a high sensitivity and a high resolution collimator is the ability to define an object at a distance from the surface of the collimator. This difference in resolution becomes clinically apparent even at distances as close as 3 cm to the face of the collimator. This is important because the heart does not lie directly on the surface of the body, but at a depth of 5 cm or more from the camera.

A typical high sensitivity collimator that may be used to image technetium-99m or thallium-201 will have a resolution at the surface that permits separation of 3 mm bars with a conventional camera. At a distance of 10 cm, the resolution will decrease so that bars separated by 15 mm are barely visible. When the same experiment is performed using a high resolution collimator, the resolution at the surface is 3 mm (but count rate has decreased by more than 75 percent); when the

source is moved 10 cm away, 8 mm bars can readily be seen. *In clinical practice, the collimator used usually is a compromise that maximizes the tradeoff between resolution needed for most studies* in nuclear medicine at a count rate that allows the study to be completed in a reasonable time (generally called an all purpose collimator).[26]

Computers

Optimal features: One advantage of nuclear techniques over conventional radiography is the ease of digitizing and thus quantifying the data emanating from the nuclear medicine camera. The computer used in cardiovascular nuclear medicine should have several features to facilitate the acquisition and analysis of data: (1) the capacity for continuous viewing of both the cardiac image and physiologic information such as the electrocardiogram during acquisition; (2) the ability to process other data while an acquisition is in progress; (3) the capacity to present images in many different sizes, in a minimum of 64 levels or colors, that are continuously variable and under the control of the operator to produce an image that the operator finds suitable for interpretation; and (4) the capacity to display several studies simultaneously (to facilitate comparison with previous examinations and to optimize the detection of changes in function). Quantitative analysis of the data is performed by the placement of regions of interest over the cardiac chambers. The computer calculates the total counts and picture elements in each area or can determine the time between events from a series of images. The generated numbers reflect either the rate of change of relative blood volume with time (in the case of blood pool images) or the regional distribution of myocardial perfusion (in the case of thallium-201 images). A computer data acquisition and analysis system should be logical to use so that any physician or well trained technologist can acquire and display data without having to resort to an instruction manual.

Acquisition of data: The acquisition of data on ventricular function can be done either with a "list mode" technique in which the data are digitized as they occur and recorded with time and physiologic event markers for subsequent formatting and analysis, or directly in "frame mode" as a multigated acquisition study. The list mode approach allows decisions about data display to be made after the completion of acquisition, the elimination of unwanted data such as ectopic beats, and the formatting of the data backwards to permit an analysis of the filling phase of the ventricular function curve. In a frame mode study, decisions must be made before acquisition about both the number of segments that are to be recorded per cardiac cycle and the range of heartbeats that are to be sampled. However, in practice eliminating a few ectopic beats or reformatting data backwards has not provided information that could not be readily obtained from conventional frame mode multigated images.

Averaging of Several Cardiac Cycles

An assumption in cardiovascular nuclear imaging is that at least several heartbeats will be needed before sufficient photons have been accumulated in the camera and computer to assess accurately structure and function. In first transit studies the data are usually summed without regard for a physiologic signal, and judgment of commencement of each cardiac cycle is made directly from count data alone. In gated studies, the start of each cardiac cycle is identified from a physiologic marker, such as the R wave of the electrocardiogram, and data from each cardiac cycle are added in the correct temporal sequence to each of the summed previous cardiac contractions. Although data can be recorded on a beat by beat basis using probes as detectors, this cannot be done with current radiopharmaceuticals and imaging devices. As a result, cardiovascular nuclear data are averages of multiple cardiac cycles. If all beats are of similar length, there are no aberrations in the data. As the number of aberrant beats increases, the recorded information is degraded and measurements such as regional wall motion may become incorrect. Arrhythmia filtering can prevent this, but will result in an increase in the time required to acquire the study.

The averaging is tolerable in most clinical situations because the duration of systole does not change linearly with cardiac cycle length. Thus, a change in heart rate from 80 to 100 beats/min results in a decrease in the systolic portion of the cycle from 340 to 310 ms (an insignificant alteration in the systolic phase). Nevertheless, when atrial or ventricular ectopic beats are more frequent than 10 percent of the total beats during gated imaging, the data recorded are degraded. However, atrial fibrillation seldom results in an impaired study if there is a regular ventricular response. One of the most difficult problems we have found has been the artifacts that are produced by a functioning pacemaker and that may result in double gating. This problem can be detected by observing the electrocardiographic tracing and physiologic trigger, where two triggers will be seen for each cardiac cycle. The problem may be overcome by moving the electrocardiographic electrodes until either the pacemaker signal or the patient's own R wave is the dominant triggering signal.

Calculation of Ventricular Function

The counts approach for the measurement of ejection fraction: This method was first performed by Parker et al.[27] These investigators placed a region of interest over the left ventricle at end-systole, a separate region over the ventricle at end-diastole, and took as background the counts in the myocardial silhouette on the end-systolic frame. The tracer data from their study correlated with area/length calculations of ejection fraction obtained at contrast angiography in the same patients. To calculate ejection fraction, the change in counts from end-diastole to end-systole was calculated and divided by the counts at end-diastole after background correction. These studies suggest that the activity seen by the detector in the left ventricle, after background correction, is linearly proportional to volume. Subsequent studies have confirmed the reliability of the counts method for measuring both ejection fraction and reconstruction of the volume curve from equilibrium gated images.[28–30]

The counts technique is not completely free of geometric considerations because of the attenuation of photons within the source at increasing depth. When the end-diastolic ventricular volume is 300 ml or less, the counts perceived by the detector are linearly related to absolute volume.[26] At volumes greater than 300 ml, there is a progressive divergence of the perceived counts and the true ventricular volume so that at 500 ml the counts method is no longer valid. Another problem with the counts method of measuring ventricular function is the need for a background correction (a problem that also limits quantification of thallium images).[31] There is no one method for correcting background that is entirely accurate—that is, one that would simulate activity arising behind the ventricle if the chamber were replaced by a nonradioactive object with the attenuation of blood and muscle. In clinical practice, the left ventricular background on the blood pool scan is approximated using a zone just posterior to the left ventricle in the left anterior oblique projection, which provides a value that corrects for Compton's scatter and the left atrial and pulmonary activity contributing to the perceived left ventricular activity.

Method of identifying the edge of the left ventricle: The method of placing the region of interest over the left ventricle is critical to the accuracy of measurement of ejection fraction and end-diastolic filling rates. If a single region placed on the end-diastolic ventricle is used for computation of the remainder of the cardiac cycle, the ventricle may shift during contraction and either the left atrium or right ventricle may appear under this region of interest. Should this occur, the calculated ejection fraction will be too low. More accurate methods track the left ventricular outline during the entire cardiac cycle and thus minimize the opportunity for erroneously including the left atrium or right ventricle in the region of interest during ventricular systole.[30]

The two common methods used for identifying the edge of the left ventricle are threshold analysis, which detects the edge of the left ventricle as a point below a percent of the peak counts in the ventricle, and measurement of a second derivative, which places the edge of the ventricle where a certain rate of change in counts occurs. The algorithm searches from the center of the ventricular blood pool, identified by the computer operator, until the preset parameters are reached, at which time the computer identifies that as an edge.[32] No method of semiautomatic edge analysis works perfectly in every patient. The final quality control of these analyses rests with the physician performing the study. If the ejection fraction calculated by the computer using semiautomatic edge detection does not match with that observed visually, the computation should be repeated and the error in computation identified. In some patients, particularly those with a large right ventricle or left atrium, the semiautomatic programs will not work at all. In these patients, the end-systolic frame should be identified visually from the cinematic presentation and a region of interest drawn manually over this image. The counts in the end-systolic region of interest should then be compared with those in an end-diastolic region of interest. After background correction, the ejection fraction may then be computed.

Evaluation of Technical Data Adequacy

Image quality: Before the images are analyzed in detail, it is important to assess the technical adequacy of the collected data. This can be done by evaluating the sharpness of the borders of the heart and the adequacy of the triggering signal. Patient motion, inadequate complexation of the technetium-99m to the red cells, marked obesity or improper setting of the scintillation camera pulse-height analyzer will all contribute to poor image quality. If the borders of the heart are well demarcated, the image should then be evaluated for the adequacy of gating.

Problems with gating: Two types of problems occur with gating—regular and irregular. Regular occurrences (those with a fixed relation to the R wave) will produce a characteristic step in the data and will appear as a sudden coarsening or decrease in the brightness of the image in the last several frames. To test for this problem, the total number of events recorded in each data frame should be evaluated. A variation of less than 10 percent in total counts/frame from the first to the last frame should be found when data from the entire field of view are recorded. (Although blood volume of the heart changes during the cardiac cycle, the atria fill out of phase with the ventricles, and the blood ejected by the heart enters the lungs and aorta, which are also in the field of view; therefore, no change in total counts should be seen.) Irregular gating disturbances in patients with a loose electrocardiographic lead, atrial fibrillation with a wide variation in ventricular response or multiple premature ventricular complexes can result in uniform data in each frame but the chambers may appear hypokinetic or akinetic. These problems should be detected and corrected during data recording.

Calculation of left ventricular volume: After the calculation of ejection fraction based on the counts approach previously described, the absolute volume of the left ventricle should be determined. Two approaches to this measurement have been suggested: (1) geometric methods from the outline of the ventricle corrected for picture element size[33]; and (2) counts methods correcting the perceived activity for attenuation.[35] Both the geometric and counts method have been validated by comparison with contrast angiographic measurements. The weakness of the geometric method is the reliance on careful definition of the borders of the left ventricle, whereas the weakness of the counts method is the requirement for a precise measurement of the attenuation in that patient. These measurements of attenuation for technical reasons, are extremely difficult to perform precisely in every patient. The combination of absolute end-diastolic volume and ejection fraction permits calculation of cardiac output and stroke volume from these tracer procedures.

After technical assessment, the study is evaluated for overall heart size and individual chamber and great vessel size and function. The approaches to making these interpretations and the reliability of the results are covered in separate articles in this Symposium.

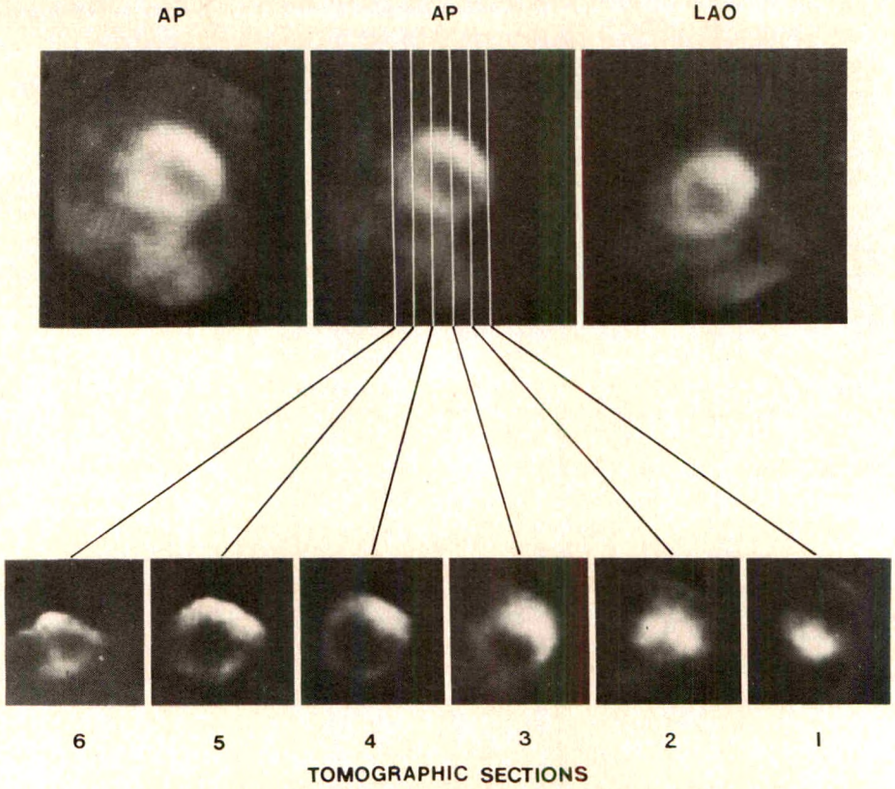


FIGURE 3. Emission planar tomogram recorded with a 25° slant hole collimator from a patient who received thallium-201. The planar images recorded with the parallel hole collimator in the anterior view (**left**) and 45° left anterior oblique (LAO) view (**right**) are shown above. The tomogram was recorded in the left anterior oblique position. The relative location of each slice is indicated on the anterior view by the **white lines.** Although the study could clearly be judged as abnormal from the planar views, the extent of abnormality in the septum and apicoinferior walls is best appreciated from the tomographic images.

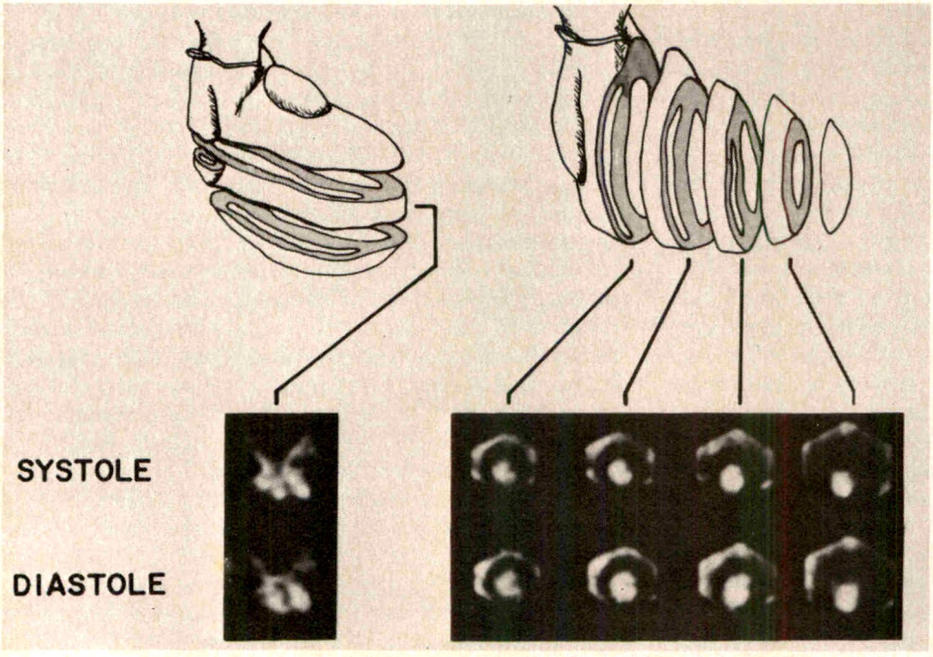


FIGURE 4. Tomographic blood pool images obtained by two different methods. **Left,** transverse sections obtained using a positron camera and carbon monoxide as the blood pool label. **Right,** tomographic sections obtained using a 25° rotating slant hole collimator in the left anterior oblique 45° projection and technetium 99-m–labeled red blood cells.

Intervention studies: Finally, once cardiac structure and function have been determined at rest, an intervention study may be indicated. Intervention images are obtained to determine if exercise, pacing or drug infusion causes changes in the expected regional and global ventricular function. Pre- and postintervention examinations are compared to detect changes in ejection fraction, regional wall motion and cardiac chamber volumes. An additional variable that can be quite useful in the analysis of interventions is an evaluation of changes in pulmonary blood volume[35] (probably a reflection of left atrial pressure).

Conclusions

The application of nuclear techniques to measurements of cardiac function is in its infancy. These techniques, which began to have clinical use in the early 1970s, have now evolved to a point where they are routinely used in many laboratories across the country. The studies provide information regarding the quality of cardiac function as well as the distribution of regional perfusion, variables that previously could only be measured by cardiac catheterization and contrast angiography. Computer processing and special collimation when recording nuclear images provide the ability to obtain tomographic data from the heart. The most common technique uses the multiaperture pinhole collimator.[36] This tomographic technique appears to improve the specificity of thallium images. Several other collimators have recently been suggested to accomplish tomographic imaging such as the fixed angle slant hole and variable angle slant hole collimators (Fig. 3). Application of the tomographic approach to gated imaging should provide some unique methods of estimating regional wall motion (Fig. 4). Although tomography cannot as yet be used for absolute data quantification (an intrinsic problem with the form of data collection and analysis), relative changes in activity from one portion of the image to another can be defined and quantified. As experience increases, the appropriate questions to ask will become more apparent and the patients who would best benefit from these procedures more clearly defined. The ability to detect abnormal cardiac function at rest or after interventions and to study outpatients as well as acutely ill patients in intensive care units adds a new dimension to clinical cardiology.

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Evaluation of the Left Ventricle With Two Dimensional Echocardiography

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Two dimensional echocardiography, because of its wide field of view, has been shown to be superior to the M mode approach for ultrasonic evaluation of the left ventricle. The use of this technique for determination of ventricular volume estimates and detection of asynergy has been promising but is limited by compromised image quality found in many patients with ischemic heart disease. Because it supplies cross-sectional information about the ventricular chamber and wall thickness simultaneously, this new technique lends itself to the anatomic localization of changes in regional performance that accompany ischemic heart disease. It allows simultaneous study of regional dynamic changes in chamber circumference, wall thickness and motion characteristics that give practical information on coronary artery disease and acute myocardial infarction.

In the past decade, M mode echocardiography has become a useful clinical approach for the evaluation of left ventricular chamber size, wall thickness and motion characteristics.[1–8] The recent development of practical two dimensional echocardiographic systems has now stimulated a renewed interest in the evaluation of ventricular performance using ultrasound because of its wide field of view and spatial integration of anatomic target information.[9]

Two dimensional echocardiography presents information in cross section, thus differentiating the informational content of the image from those derived by other methods. Cardiac images based on static (chest X-ray) or dynamic (fluoroscopic, cineventriculographic or radioisotope angiographic) approaches represent the heart and chambers as silhouettes. These techniques have been particularly successful in estimating left ventricular volume because of the overall integration of the ventricular chamber within the image. Thus, area-length determinations in one or two representative projections may be readily performed. Estimations of overall left ventricular performance such as ejection fraction can then easily be obtained.

Two dimensional echocardiography can also be used to estimate ventricular volumes with some relative success. However, echocardiographic estimates lack the overall integrative capacity of the silhouette techniques for reliably visualizing the ventricular margins in one or two ideal planes that allow for such determinations. Instead, the echocardiographer must serially visualize the ventricle in multiple viewing planes to evaluate the entire ventricular anatomy. This does not mean that two dimensional echocardiography is intrinsically less useful for evaluating left ventricular performance. On the contrary, there is no other technique that can clearly image the dynamic changes in the cardiac muscle *and* chamber size simultaneously. This unique combination of ventricular functional information should now stimulate the search for new and perhaps better descriptors of ventricular performance than have previously been available.

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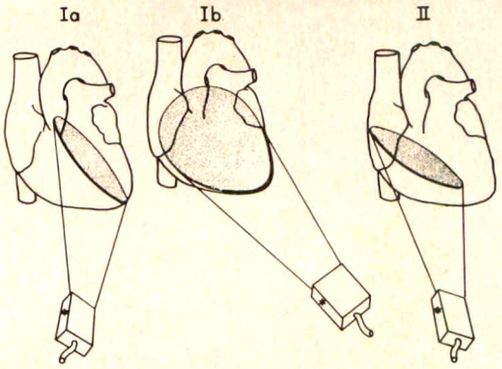


FIGURE 1. Transducer orientations for evaluation of the long axis of the left ventricle. For details, see text.

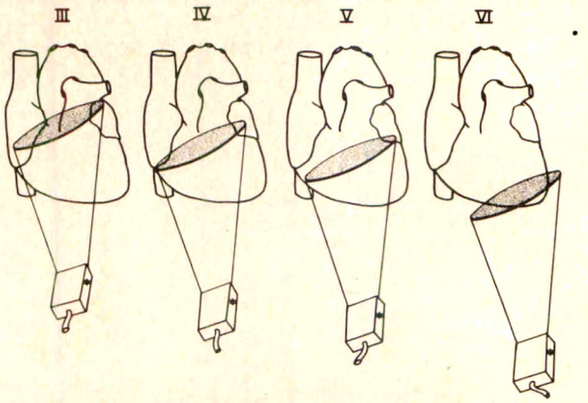


FIGURE 2. Transducer orientations for evaluation of the serial short axes of the left ventricle. For details, see text.

Echocardiographic Techniques

Long and short axis views of the left ventricle: The simplest approach for the understanding of the multiple views utilized in two dimensional echocardiography is to imagine two basic cardiac axial orientations: the long axis (Fig. 1) and the short axis (Fig. 2). Examination of the left ventricle is usually begun in the long axis (Fig. 1, panel Ia) by placing the transducer on the chest wall in the second, third or fourth left intercostal space and angling the scan plane parallel to an imaginary plane from the patient's right shoulder to the left subcostal margin. This plane intercepts the long axis of the left ventricle from the aortic root to the region of the left ventricular apex. The interventricular septum and the posterior ventricular wall can generally be evaluated in this view.

Another long axis view, termed the apical long axis or the apical four chamber view (Fig. 1, panel Ib), is obtained by placing the transducer over the ventricular apex, rotating approximately 90° clockwise and then angling cephalad through the ventricle.[10] This plane of view intercepts the apical, septal and anterolateral walls of the left ventricle.

Serial short axes of the heart may be obtained by rotating the transducer 90° in the original left parasternal long axis and then sequentially angling the interrogating plane at the level of the aortic root (Fig. 2, panel III), mitral valve orifice (panel IV), papillary muscles (panel V) and apex (panel VI). Evaluation of the left ventricular chamber in short axis is generally accomplished using the latter three views. They allow imaging of the posterolateral, anterolateral, septal and inferior walls from the base to the apex.

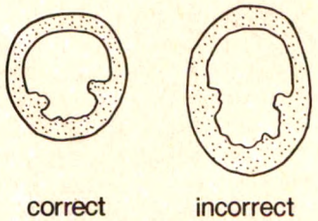


FIGURE 3. Schematic diagram showing images resulting from correct and incorrect transducer angulation. For details, see text.

Transducer angulation: Particular care must be taken during the examination procedure to angle the interrogating plane properly through the true long or short axis of the ventricle. Improper angulation of the scan plane tangentially through the ventricle will result in distortion of the appearance of the ventricular long axis. The characteristic normal elliptical configuration will then appear circular or cut off near the apex and origins of the papillary muscles. In the short axis, the problem is recognized when the normal circular appearance of the cavity in this axis appears elliptical or oval in shape (Fig. 3). In addition, the papillary muscles appear midway around the ventricular circumference rather than posteriorly, and there may be reciprocal thickening and thinning of the chamber walls on opposite sides of the ventricle.

Echocardiographic imaging system: Multiple ultrasonic systems have been devised for viewing the left ventricle in the cross-sectional format.[11] Illustrations in this manuscript were obtained using a previously described[12,13] real time, phased array imaging system. This device utilizes a handheld, 24 element transducer array that measures 14 by 24 mm at the site of skin contact and relies on phased array principles to electronically steer and focus the sound beam through the structures under investigation. Real time, cross-sectional images of cardiac structures are presented in a circular sector format 50°, 60° or 90° in azimuth at a frame rate of 30/s. Images are permanently recorded on videotape for later playback and analysis.

Much detail is lost in the single frame scan images that constitute the illustrations in this paper. They were made from videotape recordings by means of a 35 mm photograph of the sector arc in the stop frame mode. As such, there is a loss of visual integration of motion that normally accompanies real time playback. Moreover, there is a severe degradation in image quality caused by photographing a single frame from the videotape recording because an individual videotape frame represents the scan information collected in 1/60th of

a second. During operation in the 90° 160 line format, therefore, each single frame video field shows only one half (80 lines) of the information provided in the real time scan.

Estimation of Left Ventricular Volume

Several studies have shown a significant correlation between M mode echocardiographic and contrast angiographic estimates of left ventricular volumes and ejection fraction. However, it has become apparent that when the ventricle becomes grossly enlarged[14,15] or contains significant regional wall abnormalities,[16–18] the correlation with angiographic estimates of ventricular volume rapidly deteriorates. Most of the problems in estimating volumes with the M mode technique are related to the small sampling area afforded by the beam from a single stationary ultrasonic crystal. Two dimensional echocardiography, by providing more target information, could theoretically improve volume estimates. In vitro studies have shown a remarkable potential for accurate volume determinations with the cross-sectional technique. However, initial clinical studies have shown a greater variability in the relation between two dimensional and other established measures of left ventricular volumes.

Correlations with experimental measurements of ventricular volume: A recent study by Eaton et al.[19] has examined the accuracy of two dimensional echocardiography to measure the volumes of latex-filled balloons and formalin-fixed canine hearts in vitro using Simpson's rule. Simpson's rule states that volume can be calculated by dividing a three dimensional object into slices of known thickness and surface area. The volume of the object is equal to the sum of the volumes of each slice: Volume = ΣAH, where A is the surface area determined with planimetry and H is the height of each slice. By using this technique, it was found that the calculated volumes of the latex balloons and the formalin-fixed hearts correlated extremely well with direct volume measurements having correlation coefficients of 0.99 and 0.98, respectively. To approximate in vivo measurements, Eaton then used Simpson's rule to measure the volumes of isolated, cross-perfused, ejecting canine hearts and compared those values with direct measurements obtained using a volumetric displacement chamber. The correlation was again very close ($r = 0.97$).

Clinical correlations with angiocardiography: Several clinical studies have been performed to estimate left ventricular volumes. Folland et al.[20] studied various geometric models to estimate volume using two dimensional echocardiographic images and compared them with angiographic and radionuclide volume estimates. Use of a modified Simpson's rule approach with one long axis and three short axis images gave the closest correlation with angiographic volume estimates. Estimations of end-systolic volume revealed the closest agreement with single plane angiographic estimates ($r = 0.86$). Estimates of end-diastolic volume and ejection fraction showed less consistent relation to the angiographic measures. Combining all end-diastolic and end-systolic volume data points improved the correlation ($r = 0.84$), but a large standard error of the estimate (43 cc) remained. Comparison of echocardiographic and first pass radionuclide angiographic estimates of ejection fraction gave a correlation coefficient that was similar to that of the comparison of the echocardiographic and cineangiographic estimates ($r = 0.75$). The study group consisted of 35 patients, 20 of whom showed regional contraction abnormalities on cineangiography, and 8 of whom had ventricular volumes greater than 200 cc. Thus, although the relation between the estimates of ejection fraction obtained with two dimensional echocardiography and cineangiography was relatively weak, they were in much closer agreement than were those obtained with simultaneous M mode echocardiography.

A similar study recently published by Schiller et al.[21] compared biplane angiographic and two dimensional echocardiographic estimates of end-diastolic and end-systolic volumes and ejection fraction among the 30 patients. A closer relation between the two techniques was shown in this study even though the percent of patients with regional wall motion abnormalities was slightly greater than that in the previously mentioned study group. The advantage of the integrated target information provided by the two dimensional approach in comparison with the M mode approach was again demonstrated when simultaneous M mode volume estimates were compared with angiographic estimates in 23 of the patients. The intraobserver variation for cross-sectional echocardiographic volume estimates in Schiller's study varied by only ±4 percent. Interobserver variation, tested by a regression analysis of the echocardiographic volume data calculated by two different observers, yielded a correlation coefficient of 0.82, 0.95 and 0.95 for end-diastolic and end-systolic volumes and ejection fraction, respectively. Silverman,[22] Carr[23] and Schiller[24] and their co-workers all performed favorable comparisons of two dimensional and angiographic determinations of volume in small series of children and adults. The levels of inter- and intraobserver variability were acceptable in each study.

Clinical limitations of two dimensional echocardiography: Despite these findings, certain factors limit the practical utility of two dimensional echocardiography for the estimation of left ventricular volumes. Variation between in vitro and the range of in vivo correlations suggest that the difficulties imposed by viewing the heart through the intact chest wall are significant. Target acquisition and overall image quality tend to vary widely among patients. These variations represent the greatest limitation to the use of two dimensional echocardiography for routine clinical volume determinations. This is particularly true among older patients who are studied for evaluation of coronary artery disease. In a recent study[25] comparing two dimensional echocardiography with quantitative angiography for the detection of wall motion abnormalities, clinically useful information with clear visualization of isolated ventricular segments could be obtained in 89 percent of the patients. However, visualization of the

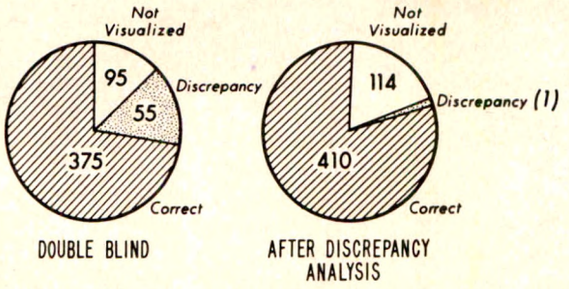


FIGURE 4. Results of double-blind analysis (**left**) and after discrepancy analysis (**right**) in comparison of two dimensional echocardiography and cineangiography in the detection of asynergy. For details, see text.

entire left ventricle could be obtained in only 60 percent of the patients. Thus, two dimensional echocardiography is clinically most useful for the analysis of segmental regions of the myocardium and is generally less effective as a global descriptor of left ventricular chamber size. To date, there has been no report of a large series in which two dimensional echocardiography was used for this purpose in a wide variety of disease states.

Imaging of the Left Ventricular Myocardium

Experimental determination of left ventricular mass: Several experimental studies were performed to attempt to quantitate the mass of myocardium more precisely with two dimensional echocardiography. Because of the lack of an adequate standard of measurement in vivo, most of these studies involved the comparison of cross-sectional in vivo estimates with direct measures of left ventricular mass at autopsy in dogs. Wyatt et al.[26] recently analyzed seven mathematical models for quantifying left ventricular mass from in vivo echocardiographic measurements in 21 dogs. Using a modified Simpson's rule model, they found an extremely close relation between ultrasonic and postmortem measurements ($r = 0.95$). They also found a similar relation using an area-length (AL) model with the left ventricle represented as an ellipsoid toward the apex and a cylinder near the base ($V = 5/6$ AL). The correlation coefficient was 0.94 with a standard error of the estimate of 11 g. Both methods allowed the data points to cluster closely about the line of identity and resulted in a percent error of only 6 ± 1 percent (mean $\pm$ standard deviation). These results have recently been confirmed by other investigators. Salcedo et al.[27] reported a correlation of 0.97 when comparing two dimensional estimates with anatomic left ventricular mass measurements in 19 dogs, whereas Schiller et al.[28] reported a correlation of 0.96 with postmortem measurements using paired long and short axis views in the dog model.

Analysis of regional wall motion abnormalities: In addition to its value in quantifying left ventricular mass, two dimensional echocardiography has also been shown to be very useful for analyzing abnormalities in regional wall motion characteristics such as those seen in ischemic heart disease. Meltzer et al.[29] utilized two dimensional analysis of regional asynergy to assess the efficacy of interventions designed to alter myocardial infarct size in dogs. They found that infusions of nitroglycerin significantly decreased, whereas phenylephrine significantly increased the percent abnormal wall motion over a period from 20 minutes to 5 1/2 hours after coronary occlusion. Control dogs given saline solution alone showed no significant change in percent wall motion abnormality after the initial 20 minutes after occlusion.

The ability of two dimensional echocardiography to detect wall motion abnormalities has been the subject of several clinical studies as well.[30,31] Using two dimensional echocardiography, Weyman et al[32] identified each of 31 patients with angiographically proved aneurysms and this approach was far superior to other common clinical indicators including electrocardiography, physical examination, chest X-ray film and M mode echocardiogram.

The relation between two dimensional echocardiographic and quantitative biplane cineangiographic localization of asynergy in human subjects has recently been defined.[25] Double-blind comparison of movement in five wall segments were compared in 105 consecutive patients undergoing cardiac catheterization (525 total segments). On double-blind analysis, 95 segments were not adequately visualized echocardiographically (Fig. 4, left panel). Among the remaining 430 segments, results of echocardiography and cineangiography agreed in 375 segments (87 percent) whereas discrepancies occurred in 55 segments (13 percent). A retrospective review of these discrepancies revealed easily recognizable reasons for the differences in 54 of the 55 discrepancies (Fig. 4, right panel). Thirty-four discrepancies were attributed to echocardiography and 15 to angiography; 6 were termed indeterminate. Of the 34 discrepancies attributable to echocardiography, 10 resulted from observer error and 19 from inadequately visualized echo targets that were previously judged adequate. Despite the care taken to position the transducer properly on the chest wall, four errors were caused by tangential angulation of the transducer. Most of the 15 angiographic discrepancies resulted from the superimposition of abnormally contracting wall regions over the normally contracting portions of the ventricle (Fig. 5); for example, when severe anterior wall asynergy was present the abnormally contracting anterior wall was superimposed over the interventricular septum in the left anterior oblique angiographic view, thus obscuring true septal wall motion. The six discrepancies termed indeterminate were so classified because they could not readily be attributed to either imaging technique.

Because the double-blind analysis revealed that inadequate endocardial targets accounted for the most frequent error by echocardiography, the echocardiograms were carefully reviewed in an effort to establish minimal criteria for assessing the adequacy of an echo

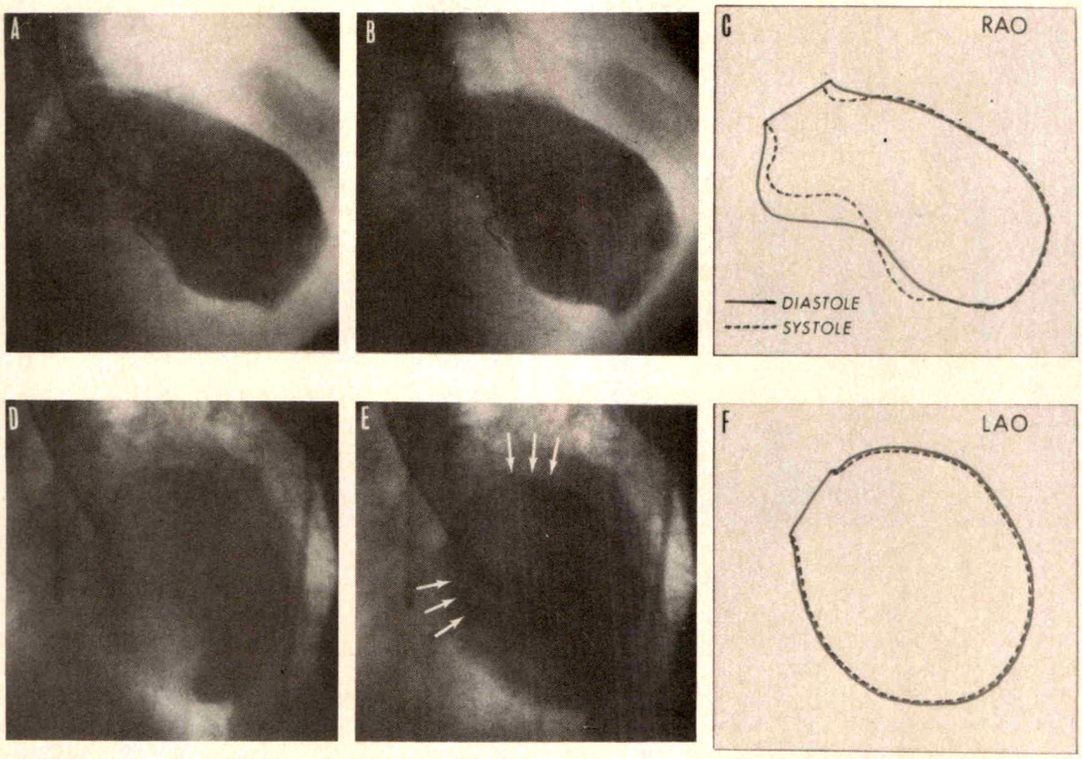


FIGURE 5. Sequential diastolic (**A** and **D**) and systolic (**B** and **E**) angiographic frames from the same patient as in Figure 6. The right anterior oblique (RAO) view is shown in **top row** and the left anterior oblique (LAO) view **at bottom.** Note the large ventricular aneurysm and contracting base in **C**. The arrows in **E** point to the contracting base, which is poorly visualized through the silhouette of the aneurysm in the left anterior oblique view (**F**). These findings were similar to those predicted by two dimensional echocardiography.

image. On review, it was clear that at least 50 percent of the endocardium in any one wall region must be visualized throughout the cardiac cycle in order to predict reliably the presence or absence of asynergy. These data indicate that accurate evaluation of the left ventricle for asynergy is possible with two dimensional echocardiography. However, proper appreciation of correct technique and the limitations of both echocardiography and cineangiography are necessary.

These findings have been supported by Heger et al.,[33] who compared echocardiographic localization of asynergy to electrocardiographic findings and evidence of necrosis at autopsy. Nineteen of 20 patients with electrocardiographic evidence of acute inferior infarction had asynergy in the posterior segments, all 14 patients with acute anterior infarction had asynergy in anterior segments, and all 3 patients with anteroinferior infarction had asynergy in anterior and posterior segments. In four patients examined at autopsy, 21 of 22 segments showing asynergy on two dimensional echocardiography also had pathologic evidence of infarction.

Quantitative determination of wall motion abnormalities in ischemic heart disease: Quantitative analysis of wall motion abnormalities has been shown to be superior to qualitative visual inspection in detecting asynergy with cineangiography.[34,35] In a recent abstract, quantitative analysis of regional wall motion abnormalities was applied to two dimensional echocardiography in the short axis views.[36] Twenty-eight patients who had undergone diagnostic cardiac catheterization were classified into two groups on the basis of (1) the presence of normal coronary arteries, or (2) the presence of proximal single vessel coronary artery disease associated with asynergy on angiographic examination. Mean and standard deviation normal values for absolute and relative end-diastolic and end-systolic wall thickness and hemiaxial shortening were determined from patients in the normal group. These measurements were obtained from 24 radii adjusted for rotation about the short axis and determined from the centroid of the left ventricle. Compared with normal subjects, patients with coronary artery disease showed abnormal (greater than 2 standard deviations) reduction in percent wall thickening (15 of 15), diminished hemiaxial shortening (14 of 15) and increased end-diastolic radius to wall thickness ratio (13 of 15) along the radii affected by the distribution of the coronary involvement.

This propensity for ischemic myocardium to thin during systole is shown in the following examples. Figure 6 shows sequential diastolic and systolic frames from the short axis of the left ventricle in a patient at rest with minor coronary obstructive disease. Systolic chamber circumference and radial shortening are normal and wall thickening is uniform. In contrast, the sequence of postexercise systolic wall thinning shown

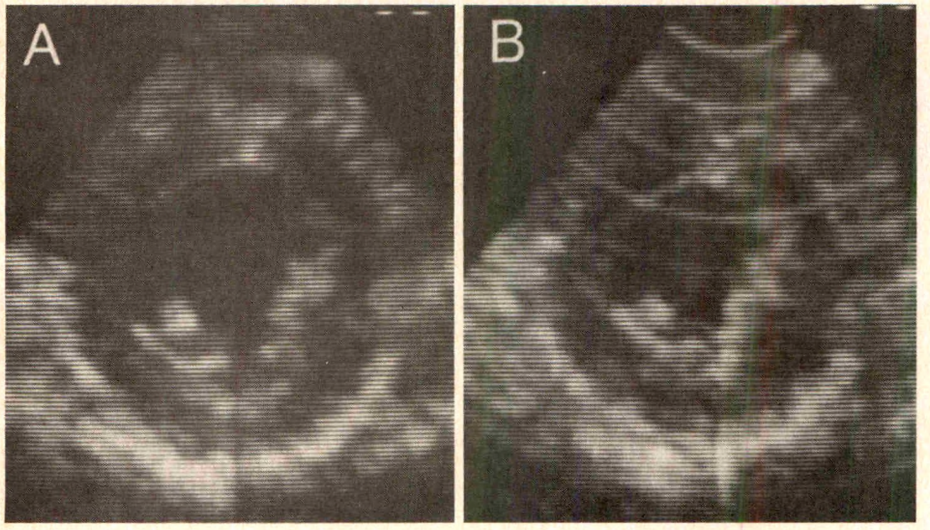


FIGURE 6. Sequential diastolic (**A**) and systolic (**B**) stop frames from a patient with minor coronary artery disease at the level of the short axis papillary muscles. Ventricular wall thickening is uniform.

in Figure 7 occurred in a patient who manifested normal thickening at rest. Subsequent cardiac catheterization revealed severe obstructive disease in a dominant circumflex coronary artery supplying the area of noted wall thinning. Despite the striking differences in these patients, practical clinical experience in assessing wall motion abnormalities by this approach is limited at the present time.

Sequential changes after acute myocardial infarction: In addition to the detection of asynergy, two dimensional echocardiography has now been used to actually observe sequential changes in the myocardium after acute infarction.[37] Eight dogs were followed up sequentially for 6 days after ligation of the mid portion of the left anterior descending coronary artery distal to the first septal perforator. Alterations in systolic radial shortening and wall thickening along 24 equidistant radii about the ventricular short axis were analyzed and compared with baseline measurements. Initial diffuse systolic radial lengthening and absence of wall thickening were noted along radii involving a segment from the anterior interventricular groove to the anterior papillary muscle. Serially, there was a progressive return of radial shortening, preceded by increased wall thickening along the margins of the involved segment. Ultimately, a well demarcated area characterized by absent systolic radial shortening and wall thickening remained where increased ultrasonic speckle and shadowing corresponded to early scar formation on postmortem examination.

This ability to detect changes in regional wall configuration after acute myocardial infarction has recently been applied to human beings. Postmortem studies[38] have shown that among patients dying within 30 days of acute infarction as many as 72 percent will show histologic evidence of regional thinning and dilatation of the infarcted area beginning within 1 week of acute infarction. This process generally occurs without his-

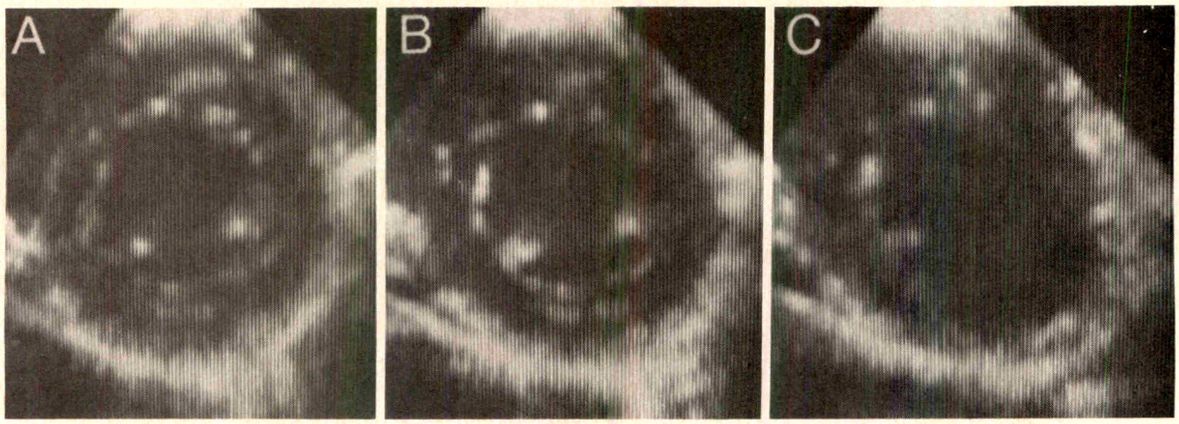


FIGURE 7. Sequential diastolic (**A**), mid systolic (**B**) and end-systolic (**C**) stop frames at the level of the papillary muscles in the short axis. The echocardiogram was obtained after exercise in a patient with severe coronary occlusive disease and shows posterolateral and inferior wall systolic thinning.

tologic evidence of infarct extension after the acute event and has been termed "infarct expansion." Pathologic evidence suggests that infarct expansion results from intramyocardial rupture of necrotic muscle fibers and appears to be of much greater hemodynamic and prognostic importance than actual infarct extension.[38,39]

Eaton et al.[40] recently used two dimensional echocardiography in an attempt to detect noninvasively significant infarct expansion in the first 2 weeks after acute infarction in 28 patients. Eight of these patients showed gross infarct expansion on echocardiography beginning within 3 days of the infarction. These patients could not be separated from the patients without significant expansion by the usual clinical indicators of the extended infarction. One important difference soon became evident: the 8 week mortality rate in the patients with infarct expansion was 50 percent whereas no deaths occurred in patients who did not have infarct expansion on serial two dimensional echocardiographic examination. It is also important to note that all the surviving patients who had been shown to have infarct expansion on echocardiography continued to have congestive heart failure after discharge from the hospital.

Clinical Use of Two Dimensional Echocardiography

These data indicate that two dimensional echocardiography can be a useful tool for the noninvasive evaluation of the left ventricle in human beings when image quality is good. The spatial integration of target information into tomographic sections of the heart provide important information regarding dynamic changes in chamber size, wall thickness and motion characteristics in real time.

Although experiments designed to test in vitro two dimensional echocardiographic measurements have demonstrated a remarkable potential for accurate analysis of chamber size and global ventricular performance characteristics of the ventricle, in vivo studies have been unable to reproduce as high a degree of precision. The major limitations to in vivo measurements have been inadequate target acquisition and an insufficient signal to noise ratio in some patients, which may prohibit adequate definition of myocardial targets. This may cause major areas of dropout in any given tomographic plane, precluding accurate global ventricular analysis. At this stage of its development, two dimensional echocardiographic assessment of the ventricle appears limited in acquiring adequate target information to allow widespread clinical use for volume determination. However, the unique capabilities of two dimensional echocardiography to study simultaneously regional dynamic changes in chamber circumference, wall thickness and motion characteristics may be more practical. It is likely that some combination of quantitative descriptors based on regional ventricular alterations will become useful.

Two dimensional echocardiography appears to provide data on hitherto unknown sequential changes in wall thickness and motion in selected patients after myocardial infarction. The ability to detect infarct expansion noninvasively may also have very important prognostic and possibly therapeutic implications. Additional improvements in evaluating patients with coronary artery disease would include extension of the preliminary study described herein with quantitation of regional wall motion abnormalities by using techniques such as hemiaxial measurements. Also, new variables based on changes in the myocardium during physiologic stress must also be explored.

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Monitoring Cardiac Function With Nuclear Techniques

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Noninvasive imaging with radioactive tracers has become widely used since its introduction in the early 1970s. Improvements continue to be made in the techniques and the clinical applications. Much of the information provided by these techniques is new. The first transit studies are used mainly in the evaluation of pulmonary transit time, detection of intracardiac shunting, evaluation of right ventricular function, measurement of ejection fraction and detection of wall motion abnormalities at rest and after exercise. The gated blood pool study is found to be most useful in assessment of global left ventricular function, regional wall motion, valve regurgitation and right ventricular function.

The techniques of nuclear cardiac imaging are noninvasive, simple, successfully performed in almost 100 percent of cases. They are easy to interpret, able to be quantified and able to be almost totally automated. Their use is likely to become more widespread in the future.

The earliest studies of the pumping function of the heart with radioactive tracers were performed over 50 years ago by Blumgart and Weiss[1] in Boston. These investigators measured the velocity of the circulation in normal persons and patients with various types of heart disease by injecting a solution of radon in one arm vein and measuring the time of arrival of the activity in the opposite arm by means of a cloud chamber. This concept was further developed in 1948 when Prinzmetal et al.[2] positioned a radiation detector over the heart and monitored the passage of a bolus dose of intravenously injected tracer as it passed beneath the detector. They called the resultant curve the radiocardiogram. Since then, major improvements made in radioactive tracers, detection equipment and data processing have greatly improved the amount of information available.

Today, radioactive tracers provide a simple noninvasive and reproducible means of monitoring both regional and global ventricular function. The studies fall into two major categories: (1) first transit studies, in which the injected bolus dose is monitored only during its first passage through the heart and great vessels, and (2) equilibrium studies, in which the tracer mixes within the blood pool before data collection. Often the two studies are combined and first transit data are collected before the equilibrium studies. Each study has its own strengths and weaknesses.

First Transit Studies[3-11]

Figure 1 shows 16 images obtained at 1 second intervals after the intravenous injection of technetium-99m–(Tc-99m) labeled red blood cells, with the face of an Anger scintillation camera placed over the heart. Although the resolution of the images is not as good as those obtained with contrast ventriculography, the anatomical relations of the cardiac chambers and great vessels can be identified as the tracer passes through the heart. Better perception of ventricular function, especially global and regional wall motion, is achieved by using a cinematic display made by recycling the images over and over again. Identification of specific structures is aided by color coding so that, for instance, all structures imaged before peak activity in the lungs are one color and those imaged after the lung peak activity another.[12]

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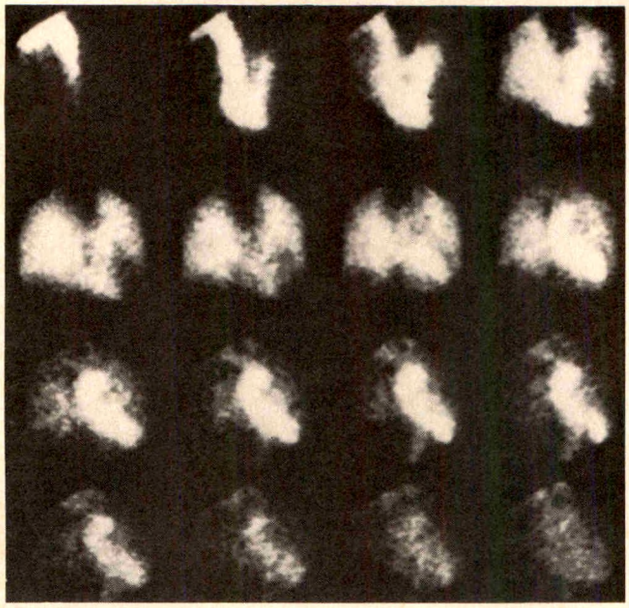


FIGURE 1. Images obtained at 1 second intervals after the intravenous injection of technetium-99m–labeled red blood cells with the detector placed over the heart of a normal person. The size and anatomic relation of the cardiac chambers, great vessels and lungs can be identified.

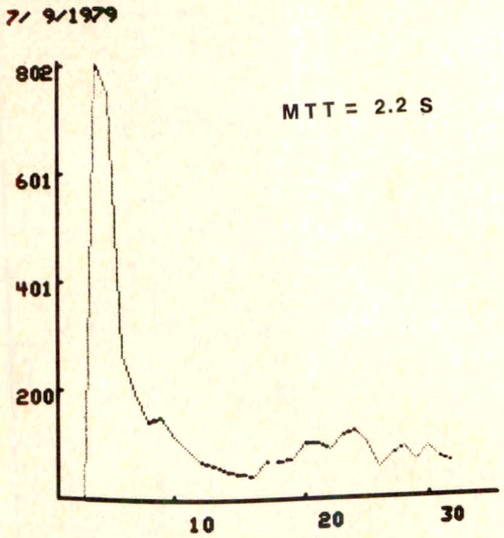


FIGURE 2. The time-activity curve of the bolus of activity in the superior vena cava. The single narrow peak indicates that the bolus was compact and adequate. MTT = mean transit time.

Figure 2 is the time-activity curve as a bolus of activity passes through the regions of interest over the superior vena cava. The adequacy of the injection is judged from this curve. Best results are achieved by keeping the volume of the injected bolus dose as small as possible and injecting through a central or large peripheral vein.[13] The full width of this vena cava curve at half its maximal value should be no greater than 2 to 3 seconds.

Figure 3 shows a series of time-activity curves; the first peak is the time-activity curve of the tracer in the right ventricle, the second peak the lungs and the third peak is the left ventricle. From these curves we calculate the mean transit times of the tracer as it passes through the cardiac chambers and the lungs.[14,15] The curve obtained from a patient with left ventricular failure showing prolongation of the bolus activity is shown in Figure 4.

In the curves shown in Figure 3, the differences in tracer activity within the right and left ventricles during systole and diastole cannot be seen because the data were acquired using 1 second intervals. A temporal resolution of 1 second per image is adequate for determination of mean and peak transit times, evaluating chamber size and the presence of shunts; but is too slow for measuring stroke volume or ejection fraction. These variables require framing rates of 50/ms or less. The 1 second framing rate is used because too few counts are recorded at 50 ms intervals to provide optimal images.[16]

Clinical Indications for First Pass Studies

The clinical indications for first pass studies include assessment of cardiac anatomy, shunt detection, differential diagnosis of dyspnea, evaluation of right ventricular function and detection of coronary artery disease.

Cardiac anatomy: The anatomic relation of the cardiac chambers and the great vessels, as well as the relative sizes of these structures, can be readily assessed from the first transit studies. Use of these data are made when assessing patients with congenital heart disease and in the initial evaluation of right or left ventricular dilatation.

Intracardiac shunt detection: First transit studies have proved useful in the assessment of intracardiac shunts.[17,18] Right to left shunting can be detected by analysis of the time of arrival of a bolus of activity in the left ventricle and aorta relative to the right ventricle. This technique is helpful in establishing the presence or absence of small shunts (1.5:1 or less).

Differential diagnosis of dyspnea: The peak and mean transit times calculated from the ventricular time-activity curves reflect cardiac output, chamber size and pulmonary blood volume. A normal pulmonary transit time at rest and with exercise rules out significant left ventricular disease, mitral valve obstruction or left atrial obstruction as the cause of breathlessness. Delayed transit times are the result of a large blood volume within a given heart chamber or within the lungs, of decreased cardiac output, or of both. Because the images themselves reveal chamber size, the relative importance of chamber dilatation and decreased cardiac output can be determined.

Evaluation of right ventricular function: It is generally accepted that the first pass study is best for assessing regional and global performance of the right ventricle. In comparison with contrast ventriculography nuclear studies do not require assumptions about the shape of the ventricle, but rely only on the difference in counts between end-systole and end-diastole for measurement of right ventricular ejection fraction.[19–22] The

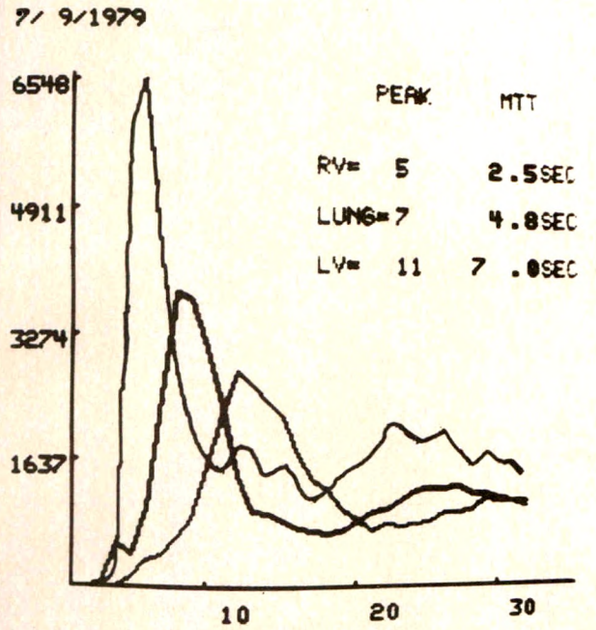


FIGURE 3. Time-activity curves generated by computer analysis of a first pass study. The first curve represents the tracer in the right ventricle (RV), the second the tracer in the lungs and the third the tracer in the left ventricle (LV). The computer identifies the time of peak activity for each chamber and calculates the mean transit time (MTT), which is a measure of the average time the tracer spends within that chamber.

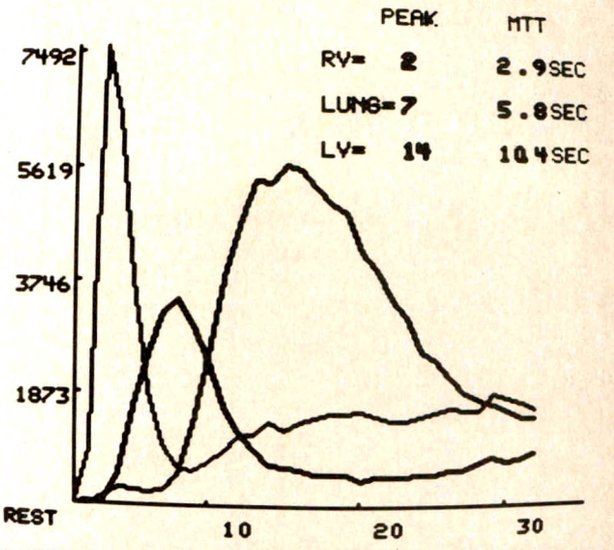


FIGURE 4. Time-activity curve of a patient with left ventricular failure. The transit of the bolus of activity through the lung (second peak) and the left ventricle (LV) is prolonged. Abbreviations as before.

first pass study, when performed in the 20° to 30° right anterior oblique projection, allows temporal separation of the right ventricle from left-sided structures and from the right atrium. With use of this technique it is possible to determine end-systolic and end-diastolic volumes, ejection rates and ejection fraction as well as to detect regional wall motion abnormalities.[23]

Detection of coronary artery disease: Studies of ventricular function at rest, whether invasive (contrast ventriculography) or noninvasive (echocardiography), are poor indicators of the presence of coronary artery disease. Nuclear studies at rest are no exception.[24] Ejection fraction and regional wall motion may remain within normal limits despite the presence of significant coronary arterial stenosis. Comparison studies of findings at rest and during stress have helped to improve the sensitivity of nuclear techniques in the detection of coronary atherosclerosis.[25,26] Using the first pass technique and comparing ejection fraction and regional wall motion from a left ventricular angiocardiogram obtained at the beginning of exercise with that obtained at peak exercise, we can detect the presence and assess the severity of coronary artery disease by observing exercise-induced wall motion defects or a failure of the ejection fraction to increase, or both. The first pass studies have the important advantage of being able to be performed within a short period of time. They have the disadvantage that each set of measurements requires an intravenous injection.

Equilibrium Blood Pool Imaging

Ventricular function studies are also performed after the blood pool tracer has equilibrated within the vascular pool.[27–29] After a single injection of Tc-99m–labeled red blood cells it is possible to record gated blood pool images for up to 4 hours, allowing the acquisition of multiple images from various projections and permitting the study of ventricular function before and after an intervention.[30–35]

Gated blood pool imaging: Equilibrium studies record data from 100 to 200 beats to form an average or composite cardiac cycle. The data from each beat are combined using the QRS complex of the electrocardiogram as a time reference point. Synchronization of the scintillation camera images with the patient's electrocardiogram is often called "gated blood pool imaging." When the technique was first developed, gated blood pool scans were recorded only at end-systole and end-diastole. It is current practice to divide the R-R interval into 12 to 64 time intervals. Useful data may be obtained using the smaller number of intervals, but for accurate derivation of all potential data, 64 time frames are best.[16,36] Successful gating is dependent on a relatively constant duration of the cardiac cycle or on the computer's ability to select only those R-R intervals that are within a given range, usually 10 or 20 percent of the mean R-R interval. Arrhythmias characterized by R-R intervals outside these limits result in images that are unreliable in revealing regional wall motion and underestimate ejection fraction.

It is customary to obtain gated blood pool images in two projections, anterior and 40° left anterior oblique. These two views are selected because, taken together, they show most segments of the left ventricle; the 40° left anterior oblique view is usually perpendicular to the intraventricular septum and therefore produces good separation of left and right ventricles (Fig. 5). If this is not the case, the positioning of the patient is adjusted until it does.

Although these two projections are adequate for most purposes, it must be remembered that (1) Neither

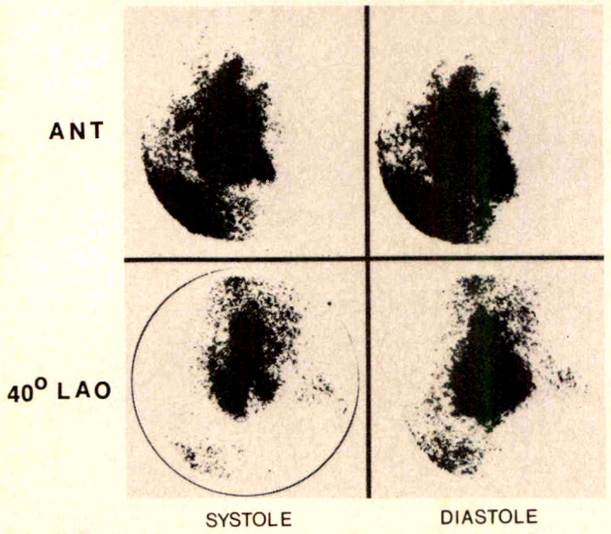


FIGURE 5. Gated blood pool studies are usually obtained in the anterior (**top**) and 40° left anterior oblique (**bottom**) views because they show all segments of the left ventricle, and the left anterior oblique view (**bottom**) produces good separation of the left and right ventricles. The ventricular volumes at end-diastole and end-systole may be appreciated in these views. These images indicate good contraction in a normal heart.

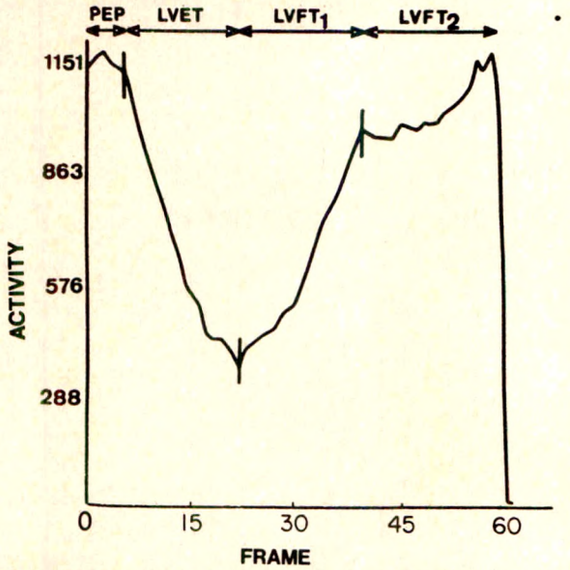


FIGURE 6. A time-activity curve obtained by summing several hundred heart beats from a gated blood pool study. The cardiac cycle has been divided into 64 frames. LVET = left ventricular emptying time; $LVFT_1$ = the fast left ventricular filling time; $LVFT_2$ = the slow left ventricular filling time (the rise in the curve at the end of $LVFT_2$ represents atrial systole); PEP = pre-injection period.

view gives good separation of atria and ventricles, since much of the right atrium underlies the right ventricle in all views except the right anterior oblique; (2) the four valve planes are difficult to locate with consistent accuracy; (3) the proximal aortic root is often difficult to see because it is overlapped by the right ventricular infundibulum and main pulmonary artery; and (4) in cases with predominant right ventricular enlargement the 40° oblique view produces inadequate separation of the ventricles because of posterior displacement of the left ventricle. A 60° image will usually resolve this problem.

Derivation of data: Data collection from a gated blood pool study can be presented as a series of images, in which each frame represents a portion of the cardiac cycle. Perception of defects is easier when the images are viewed as a cine film,[37,38] which is made by displaying the original series of images as a continuous loop. Qualitative and quantitative data are then derived. In viewing the cine display of the gated blood pool study, we ask these questions: Is the positioning of the patient correct? Is the technique adequate? Has there been proper synchronization? Do the events in the cardiac cycle take place at the proper time? Do the ventricles contract simultaneously? What are the relative chamber sizes? Is the septum thick? Are there abnormalities of regional wall motion? What is the overall left and right ventricular function? What is the state of the pericardial space?

Quantitative data are then obtained to supplement the subjective interpretation of the images (*Fig. 6*). After regions of interest are selected, computer algorithms are used to calculate systolic and diastolic volumes, ejection fraction and stroke counts. Because the labeled red blood cells are in structures other than the ventricles, background must be subtracted. The area often selected is adjacent to the free wall of the left ventricle but away from the descending aorta and above the spleen.[39] The quantitative data obtained include ventricular time-activity curves, ejection fraction, right to left ventricular stroke count ratios and ventricular volumes at different stages of the cardiac cycle.

The left ventricular data obtained with nuclear techniques agree closely with those of contrast angiography.[6,8,9,21,22,40–46] However, further validation of right ventricular data is needed. Computer techniques employing Fourier analysis, deconvolution and automatic selection of regions of interest aid in defining background, overlapping of heart chambers and accurate calculation of ventricular volume.

Analysis of the left ventricular time-activity curves yields the following indexes of cardiac function:

1. Ejection fraction (EF)
2. Preejection period (PEP)
3. Left ventricular emptying time (LVET)
4. Fast left ventricular filling time ($LVFT_1$)
5. Slow left ventricular filling time ($LVFT_2$)
6. Preejection period/left ventricular emptying time (PEP/LVET)
7. Ejection fraction/left ventricular emptying time (EF/LVET)

In patients with hypertension there is a prolongation of the $LVFT_1$/R-R and shortening of the $LVFT_2$/R-R ratios, whereas the PEP/R-R and PEP/LVET ratios remain normal. Patients with congestive heart failure show prolongation of the PEP/R-R and PEP/LVET ratios. Patients with myocardial infarction show prolongation of the $LVFT_1$/R-R ratio. The rate of ejection

of blood from the left ventricle (EF/LVET) tends to be normal in patients with hypertension, but diminished in some other forms of heart disease.[39,47]

Figure 7 illustrates the time-activity curves obtained in normal persons and patients with various types of heart disease. The time-activity curve from a hypertensive patient shows relative prolongation of fast filling time ($LVFT_1$) and shortening of the diastasis and atrial systole ($LVFT_2$). The curves of patients with left ventricular failure resulting from ischemic heart disease and cardiomyopathy show relative prolongation of the preejection period and an increased PEP/LVET ratio. Pre- and postoperative studies in a patient with aortic stenosis (Fig. 8) disclosed LVET/R-R to be elevated preoperatively (0.40) but decreased after surgery (0.27). Ejection fraction increased from 39 to 69 percent and the rate of left ventricular ejection more than doubled (from 1.24 preoperatively to 3.29 postoperatively).

Valve regurgitation can be assessed by comparing right and left ventricular stroke volumes.[48,49] In the absence of valve regurgitation, the stroke volume of the right ventricle is equal to that of the left. For patients with aortic or mitral regurgitation, the stroke volume of the left ventricle is greater than that of the right. The ratio of left to right ventricular stroke volumes in patients without regurgitation is usually slightly greater than 1 because a small portion of right atrium is included in the right ventricular region of interest.

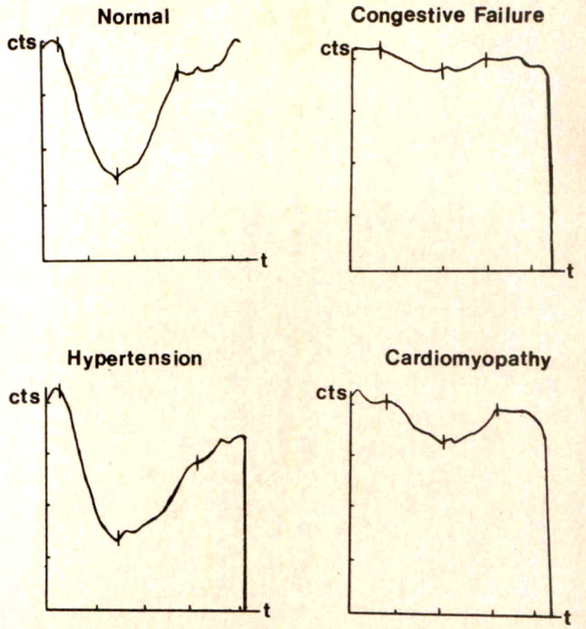


FIGURE 7. Time-activity curves in a normal patient, a patient with congestive heart failure (whose preejection period is prolonged and ejection fraction low), a patient with hypertension whose fast filling time is prolonged and diastasis is short, and a patient with cardiomyopathy whose preejection period is prolonged and ejection fraction low.

Clinical Indications for Gated Blood Pool Studies

Nuclear cardiovascular techniques have been found most useful in (1) assessment of global myocardial function (ejection fraction and wall motion); (2) assessment of global and regional left ventricular function with exercise; (3) simultaneous assessment of right and left ventricular performance.

They have also been used for (1) measurement of ventricular size; (2) measurement of ventricular volumes; (3) measurement of septal thickness; (4) assessment of septal motion; (5) measurement of valve regurgitation.

They are currently under study for (1) measurement of atrial size; (2) detection of pericardial effusion; (3) assessment of ventricular hypertrophy.

Left ventricular function: Equilibrium studies have been utilized within the coronary care unit in order to manage patients who experience shock. The gated blood pool study can quickly demonstrate the relative contribution of heart disease as opposed to that of other factors. In shock associated with inferior myocardial infarction the equilibrium study provides evidence of right ventricular infarction.[50] In the case of late shock after myocardial infarction, the studies can distinguish ventricular septal defects from mitral regurgitation by demonstrating either a shunt in the lung time-activity curve or by revealing an abnormal left ventricular/right

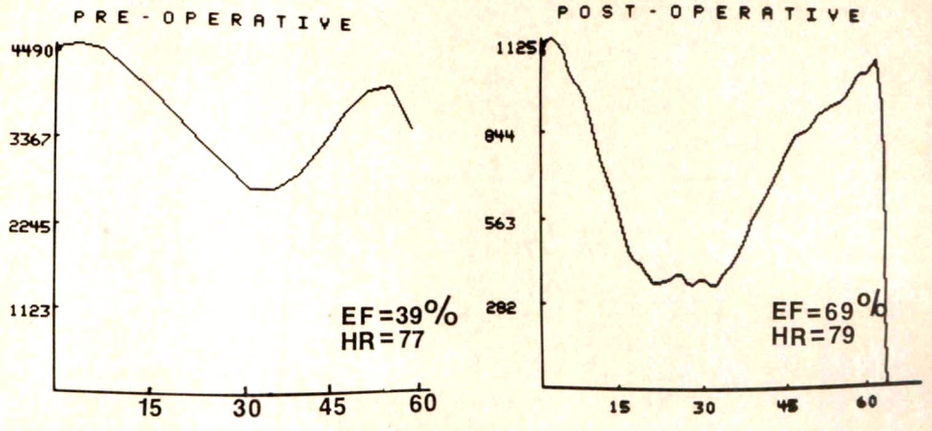


FIGURE 8. Preoperatively a patient with aortic stenosis showed a prolonged preejection period and slow emptying of the left ventricle. Postoperatively the preejection period has returned to normal, the emptying time has shortened and the ejection fraction (EF) has risen from 39 to 69 percent. HR = heart rate.

ventricular stroke count ratio that indicates valve insufficiency.

In patients with coronary artery disease, but no evidence of transmural infarction, global function is frequently normal at rest. In these patients during maximal exercise, ejection fraction and end-systolic and end-diastolic volumes are affected in a predictable manner. The usual pattern observed in patients with coronary artery disease is that the ejection fraction fails to increase and both end-systolic and end-diastolic volumes increase, whereas in normal persons the ejection fraction increases steadily with increasing work load and the end-systolic and end-diastolic volumes decrease.[51–54]

In patients with myocardial infarction or severe coronary stenosis gated blood pool studies at rest may show all grades of wall motion abnormalities, from hypokinesia to akinesia and frank aneurysm formation.[55,56]

For evaluation of patients with left heart failure from known or suspected coronary artery disease, a gated blood pool study should be performed. The equilibrium study is the ideal tool for screening possible surgical candidates. In the presence of diffuse myocardial impairment the preservation of even partial wall motion in an area of known infarction makes coronary bypass grafting to that area a possibility because motion suggests the presence of viable myocardium. Patients with poor global function and an ejection fraction of less than 30 percent are known to have a high surgical mortality rate. In the presence of septal akinesia or dyskinesia surgical repair of an anterior wall aneurysm is not usually possible. Patients with left heart failure who are shown to have moderately sized areas of akinesia or dyskinesia associated with relatively well preserved motion in the remainder of the ventricle make the most likely surgical candidates.

Right ventricular function: Right ventricular angiography is rarely performed, and simultaneous visualization of both the right and left heart chambers was not possible before the advent of nuclear studies. Studies of right ventricular function using first pass or gated blood pool studies have revealed several important findings: (1) In chronic obstructive pulmonary disease the right ventricle is dilated in less than 25 percent of patients despite the presence of respiratory failure as diagnosed by blood gas determinations.[57] (2) The greatest degree of right ventricular enlargement is seen in patients with restrictive lung disease and those with long-standing rheumatic valvular heart disease. (3) A relatively large proportion of patients have some degree of right ventricular dysfunction after anterior or inferior myocardial infarction. In patients with inferior infarction the dysfunction is predominantly the result of infarction of the right ventricular free wall. In patients with anterior myocardial infarction, the right ventricular dysfunction is secondary to septal infarction and/or associated left heart failure.[58–61]

Valvular heart disease: Nuclear studies aid in the assessment of valvular heart disease. Mitral stenosis can be suspected if there is a combination of right ventricular and left atrial enlargement, and prolonged pulmonary transit times in the presence of normal left ventricular function. The relative contributions of mitral stenosis and deficient left ventricular function to the prolongation of pulmonary transit can be assessed by looking at global left ventricular function. The severity of mitral or aortic regurgitation can be assessed from stroke (left ventricular/right ventricular) ratios. Mild regurgitation correlates poorly with angiographic estimates, but the correlation of moderate and severe incompetence is high.[48]

The timing of surgical intervention in patients with valve regurgitation, particularly aortic incompetence

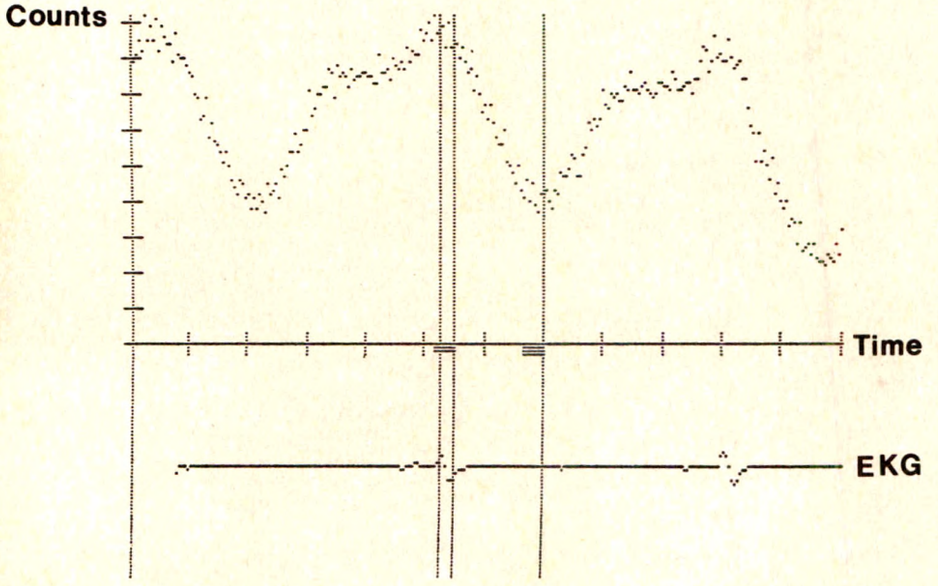


FIGURE 9. A beat to beat time-activity curve obtained with a single crystal nuclear probe. EKG = electrocardiogram.

has always been difficult. It has been suggested that periodic review of these patients with gated blood pool scans performed at rest and during exercise may be a useful diagnostic test.[62] Despite a normal or high ejection fraction at rest, a failure of the ejection fraction to increase significantly with stress may prove to be the earliest sign of deteriorating left ventricular function.

Pericardial disease: Unless present in large amounts, pericardial fluid is difficult to diagnose with certainty on gated blood pool studies. If present to any significant degree it will appear as a halo surrounding the ventricles. Localized or loculated effusions appear to be smaller, well demarcated and attached to a portion of the left ventricle. These are usually just incidental findings.

Pericardial constriction and restrictive (infiltrative) cardiomyopathy may present with similar clinical features. A gated blood pool study can help distinguish the two. In each, a prolonged pulmonary transit time is found together with an apparent halo surrounding the ventricles. In pericardial constriction the ejection fraction is normal and the interventricular septum is not hypertrophied, whereas in the patient with restrictive myopathy the ejection fraction is low and the interventricular septum is thickened.

Bedside Monitoring of Ventricular Function

It is possible to generate a beat to beat time-activity curve with the use of a single crystal nuclear probe coupled to a small processing unit (Fig. 9). The nuclear stethoscope, as the device is called, is capable of producing a beat to beat ejection fraction as well as a measure of end-systolic and end-diastolic volumes, from changes in left ventricular counts.[63,64] This device is small, readily portable and simple to use. It is an ideal tool for use in studies requiring continuous monitoring or in intervention studies.

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Ventricular Aneurysm: Cross-Sectional Echocardiographic Approach

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Current angiographic indexes of ventricular function have proved inadequate for prognostication in patients with ventricular aneurysm. Cross-sectional echocardiography can visualize residual myocardium in all four walls of the left ventricle. A new echocardiographic technique of calculating residual myocardium is presented. The echocardiographic technique yielded identical information to that of contrast angiography ($r = 0.97$). An index of residual myocardium was generated from the cross-sectional echocardiogram that correlated with the clinical state of the patients. In patients treated medically it predicted those patients likely to die within 6 months ($p < 0.005$). Preliminary observations in patients having aneurysmectomy revealed that there were good surgical results in those with an index of residual myocardium of 0.42 or greater, but more patients are necessary to establish the lower limit of a surgically acceptable level of residual myocardium.

Assessment of residual myocardium appears to be important in the management of patients with ventricular aneurysm.[1–3] However, standard hemodynamic and angiographic indexes have not proved sufficiently accurate to prognosticate patient response to aneurysmectomy.[2–5] In fact, there is little information on the natural history of ventricular aneurysm[6,7] since the introduction of modern surgical techniques.

Cross-sectional echocardiography has been shown to be accurate in the detection of ventricular aneurysm.[8] With visualization of all four ventricular walls, this procedure offers advantages in the assessment of residual myocardium.[9] In this report we present a new method for quantitating residual myocardium with cross-sectional echocardiography and we examine the prognostic value of this index in surgical and medical treatment.

Methods

Patients: Thirty-seven consecutive patients with ventricular aneurysm were studied, 32 by both contrast angiography and cross-sectional echocardiography and 5 by cross-sectional echocardiography alone. Ventricular aneurysm was considered to be an akinetic or dyskinetic area which protruded beyond the normal ventricular contour on the end-systolic frame of the echocardiogram.[10] There were 31 men and 6 women whose age ranged from 35 to 71 years (mean 60). All patients had angiographic or clinical evidence of coronary artery disease.

The presence of congestive heart failure was assessed at the initial echocardiographic study and classified according to the New York Heart Association.[11] Survival data were determined in both medically and surgically treated patients 6 months later.

Left ventriculography: This procedure was performed by way of the femoral or brachial artery in a 30° right anterior oblique view and recorded on 35 mm film at 60 frames/s. Coronary arteriography followed left ventriculography.

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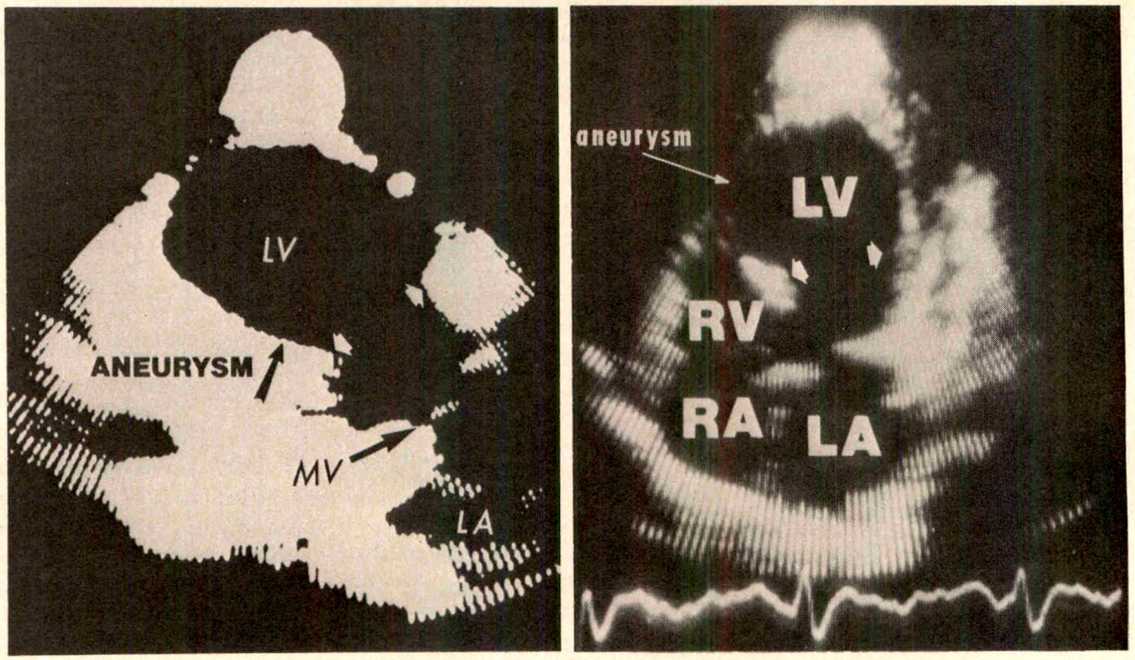


FIGURE 1. Cross-sectional echocardiograms. **Left,** apical long axis (right anterior oblique equivalent) view. A large apical aneurysm is present **Right,** four chamber apical view. A large apical aneurysm is present (**long arrow**), but the residual myocardium present in the interventricular septur and posterolateral wall is visualized (**short arrows**). LA = left atrium; LV = left ventricle; MV = mitral valve; RA = right atrium; RV = right ven tricle.

Cross-sectional echocardiography: This procedure was performed with use of a commercially available 84° phase array sector scanner (Varian 3000). Patients were examined in a left lateral decubitus position with the transducer at the cardiac apex. Echocardiographic images were recorded with a videotape recorder (Sanyo VTC 7100) at 30 frames/s using a 15 cm field. An apical long axis view (right anterior oblique equivalent) (Fig. 1, left) as well as a four chamber apical view (Fig. 1, right) was obtained in all patients. Cross-sectional echocardiography was performed within 5 days of angiography.

Ventricular measurements: To compare cross-sectional echocardiography and contrast angiography, independent observers analyzed the right anterior oblique projection and its echographic equivalent in the following manner. Calculation of residual myocardium was based on the discrete change in wall motion seen at the edge of an aneurysm. For each ventricular wall a breakpoint was identified separating the normally moving myocardium from the aneurysmal segment. With use of the end-systolic frame, a line was drawn from this breakpoint perpendicular to the long axis of the left ventricle (Fig. 2). The distance from the mitral ring to the perpendicular represented the amount of residual myocardium for each wall. This distance was expressed as a fraction of the long axis of the left ventricle. The anterolateral and the inferior walls were averaged to yield an index of residual myocardium in the right anterior oblique projection of the angiographic and echocardiographic images. In the four chamber apical view of the cross-sectional echocardiogram the same procedure was followed for the interventricular septum and the posterolateral wall (Fig. 3). For each patient the amount of residual myocardium in the apical long axis view (right anterior oblique equivalent) was averaged with that in the four-chamber apical view and a single index of residual myocardium was generated. This index reflected a contribution from all four ventricula walls.

Results

Contrast angiograms were obtained in 32 patients an complete cross-sectional echocardiograms were ob tained in 37 patients. In no patient was either techniqu inadequate for technical reasons. Figure 4 shows th correlation of the amount of residual myocardium de termined by angiography in the right anterior obliqu

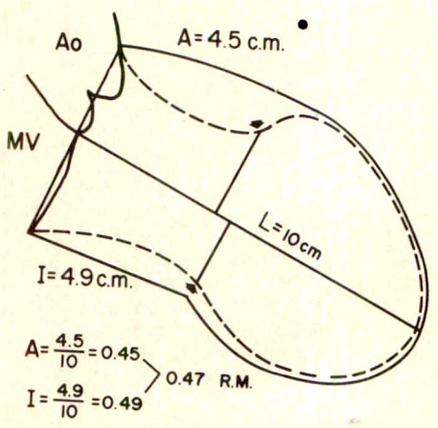


FIGURE 2. Line drawing showing how residual myocardium (R.M.) wa calculated in the right anterior oblique view of the ventricular angiogra and its echographic equivalent. A = anterolateral wall; Ao = aorta; = inferior wall; L = long axis; MV = mitral valve.

view and by cross-sectional echocardiography in the apical long axis (right anterior oblique equivalent view) (r = 0.97). There was no significant difference between the two techniques (p <0.02).

A single index of residual myocardium representing all four walls, generated from cross-sectional echocardiography, was compared with the clinical status of the patients at the time of their initial evaluation. Patients were classified into two groups: (1) those with significant congestive heart failure (New York Heart Association classes III and IV), and (2) those with little or no congestive heart failure (New York Heart Association classes I and II). A rank sum test revealed a significant difference (p <0.005) between the index of residual myocardium of these two groups, 0.61 ± 0.09 versus 0.36 ± 0.08 (mean ± standard deviation) (Fig. 5).

Predictive value of index of residual myocardium: The outcome of 25 patients treated medically is shown in Figure 6. The index of residual myocardium of patients not surviving 6 months is significantly lower (p <0.005) than that of those who did survive. The mean index in the nonsurvivors was 0.26 ± 0.05, and all pa-

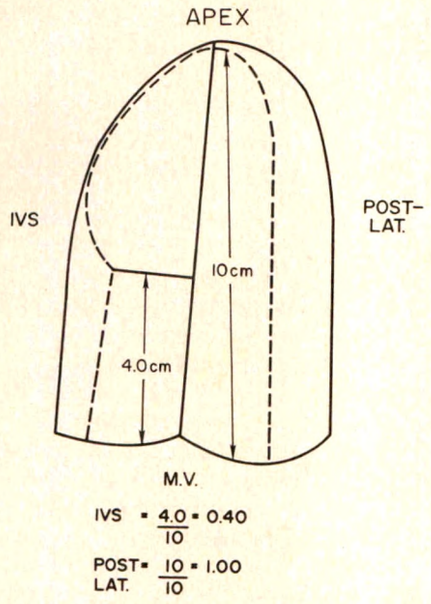


FIGURE 3. Line drawing showing how residual myocardium was calculated in the four-chamber (hemiaxial) apical view of the cross-sectional echocardiogram. IVS = interventricular septum; M.V. = mitral valve; POST LAT. = posterolateral wall.

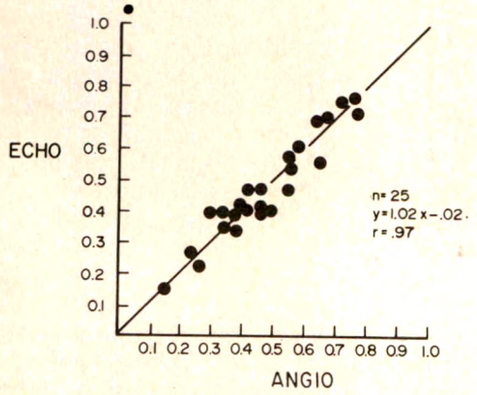


FIGURE 4. Comparison of the residual myocardium determined in 25 patients by angiography (ANGIO) (**horizontal axis**) and the cross-sectional echocardiogram (ECHO) (**vertical axis**) in the right anterior oblique projection. MV = mitral valve; RAO = right anterior oblique; RM = residual myocardium.

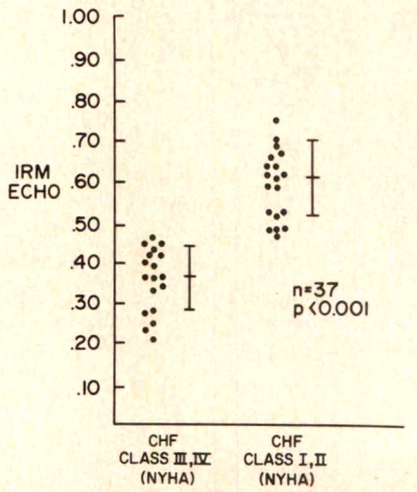


FIGURE 5. Comparison of the echocardiographic index of residual myocardium (IRM ECHO) with the clinical status of the patients. CHF = congestive heart failure; IRM = index of residual myocardium; NYHA = New York Heart Association. n = number of patients; p = probability.

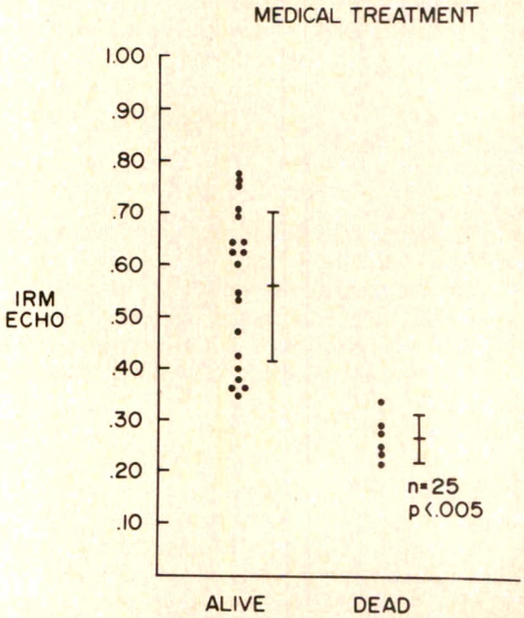


FIGURE 6. Predictive value of the echocardiographic index of residual myocardium (IRM ECHO) for 6 month survival in 25 patients treated medically.

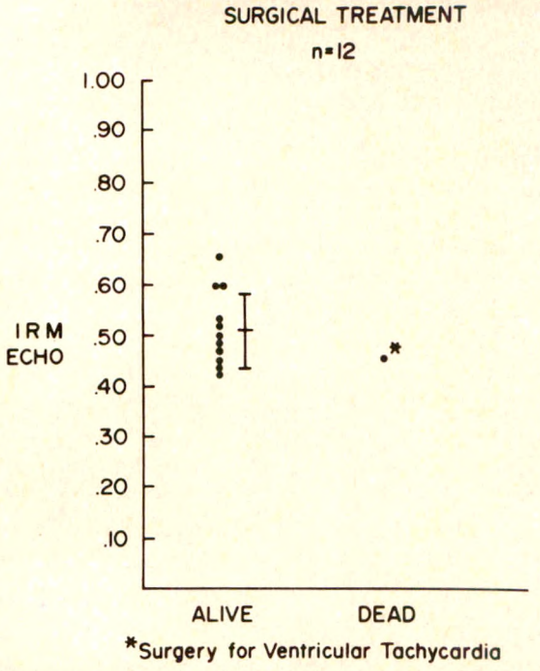


FIGURE 7. Preliminary results in 12 patients treated surgically. The one surgical death occurred in a patient subjected to a prolonged surgical procedure to ablate an arrhythmogenic focus. IRM = index of residual myocardium.

tients had an index below 0.33. Death was attributed to congestive heart failure in all six patients. In the group alive at 6 months the mean index of residual myocardium was 0.54 ± 0.16. Patients with an index below 0.50 were significantly limited by their congestive heart failure.

Twelve patients had aneurysmectomy with coronary bypass surgery (Fig. 7); in seven of these patients the primary indication was angina. Eleven patients are alive and in improved condition postoperatively; three patients with an index of residual myocardium between 0.42 and 0.44 had sufficient residual myocardium to benefit from aneurysmectomy.

Discussion

Role of functional residual myocardium and its evaluation: The importance of residual ventricular function in the treatment of patients with ventricular aneurysm has been recognized for some time.[1–3] Hemodynamic and angiographic indexes of overall function, such as cardiac output,[3–4] ejection fraction[3–6] and left ventricular filling pressure,[4,5] have been extensively examined and found to be of only marginal prognostic value. Earlier reports[12,13] examined the effect of the aneurysmal segment size on subsequent clinical course and operative results. More recent studies[1–4] have emphasized the importance of functional residual myocardium in predicting a favorable surgical outcome.

Accordingly, special methods have been proposed to evaluate residual myocardium in patients with ventricular aneurysm. Watson et al.[14] proposed a hemispheral ejection fraction to predict those patients likely to benefit from surgical intervention. Results of this method in a larger group of patients[6] failed to predict successful surgical outcome. Lee et al.[15] used a spherical model to calculate excess angiographic ejection fraction, which was combined with a coronary jeopardy score to stratify patients into high and low risk groups. There was considerable overlap between patients who responded well to surgery and those who did not. Both of these methods are derived from the right anterior oblique view alone and, therefore, do not account for residual myocardium in the interventricular septum and posterolateral wall.

Advantages of cross-sectional echocardiography: This method offers two advantages in the assessment of residual myocardium in patients with ventricular aneurysm. First, it is accurate in the delineation of normal wall motion. The characteristic breakpoint between normal and aneurysmal segments facilitates the measurement of residual myocardium. Comparison with angiography in this study revealed no statistical difference between these two techniques in the right anterior oblique projection.

Second, cross-sectional echocardiography can quantitate the residual myocardium in the intraventricular septum and posterolateral walls. The entire length of these walls is visualized in the four chamber apical view. Thus, a single index of residual myocardium is obtained that represents the residual myocardium in all four ventricular walls. This index reflects global residual myocardium in a way not previously possible.

Correlation with clinical status and operative results: The results of our echocardiographic measurement of residual myocardium are concordant with the presence or absence of important congestive heart failure. This is consistent with previous studies[13,16] correlating the extent of muscle damage with symptomatic status. More importantly, in patients treated medically, the index of residual myocardium by cross-sectional echocardiography predicts 6 month mortality of patients with aneurysm with a high degree of certainty. This prognostic information identifies a high risk group of patients in whom aggressive management should be considered.

Finally, in a preliminary group of patients having surgical correction, the index of residual myocardium has demonstrated that patients with as little as 42 percent of their myocardium contracting normally can have successful aneurysmectomy. This small group does not precisely define the lower limit of surgically acceptable residual myocardium (no patients with an index below 0.42 had surgery). More patients are needed to establish the minimal amount of residual myocardium necessary for successful surgical results.

In summary, cross-sectional echocardiography quantitated residual myocardium in all four ventricular walls. Results correlated well with both angiographic findings and clinical status. The echocardiographic index of residual myocardium predicted 6 month mortality in patients treated medically.

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Scintigraphic Evaluation of Left Ventricular Aneurysm

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Gated cardiac blood pool scintigraphy is a noninvasive method to assess regional and global left ventricular function in the patient with suspected true or false left ventricular aneurysm after a myocardial infarction. The procedure is easy to perform and provides reproducible, high resolution images that can accurately distinguish regional from diffuse contractile abnormalities often present after myocardial infarction. An overall accuracy rate of 96 percent for detection of left ventricular aneurysm can be obtained with gated cardiac blood pool scintigraphy as compared with contrast left ventriculography. The procedure also permits assessment of functional reserve of the noninvolved myocardium and thus can provide valuable information on whether enough viable myocardium will remain after aneurysmectomy. The addition of thallium-201 myocardial perfusion scintigraphy may aid in the separation of viable from scarred myocardium at the edge of the aneurysm. Both radionuclide techniques are well suited for screening the patient after infarction with persistent congestive heart failure, malignant arrhythmia or systemic emboli in whom a left ventricular aneurysm may have developed.

An aneurysm of the left ventricle can be angiographically defined as a motion abnormality of the myocardium, which is either noncontractile (akinetic) or paradoxically expanding in systole (dyskinetic).[1,2] True left ventricular aneurysm occurs in 15 to 35 percent[2,3] of patients with myocardial infarction. Less common causes of true aneurysm include myocardial abscess, trauma, erosive bacterial endocarditis and congenital defects.[4] False left ventricular aneurysm occurs much less frequently and results from rupture of the left ventricular myocardium into the pericardium without rupture of the pericardial sac. A false aneurysm is usually caused by transmural myocardial infarction although it may be related to prior cardiac surgery or trauma.[5–7]

Clinically, patients with either a true or false aneurysm present with congestive heart failure, postinfarction malignant arrhythmia or systemic emboli. The separation of a true from a false aneurysm has important prognostic implications for the patient after a myocardial infarction. In one study of 102 patients with true aneurysm the 5 year mortality rate was 88 percent, with deaths caused by congestive heart failure, myocardial infarcts or systemic emboli.[3] Although true aneurysm has a small likelihood of rupture, false left ventricular aneurysm has a 45 percent incidence rate of rupture.[5–7] Corrective surgery plays an important role in the treatment of patients with either a true or a false aneurysm. In one series of 392 patients with a left ventricular aneurysm surgically resected, the 4 year survival rate was 76 percent.[8] The mortality rate for left ventricular aneurysmectomy in both the immediate and long-term postoperative period has ranged from 0 to 40 percent depending on the size of the aneurysm, functional reserve of the noninvolved myocardium and presence or absence of congestive heart failure.[9–13]

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TABLE I

Comparison of Gated Cardiac Blood Pool Scintigraphy to Contrast Left Ventriculography for Evaluating Left Ventricular Aneurysm

Investigator	Scintigraphic Technique	Comparison With Contrast Left Ventriculography
Zaret et al.[21]	GCBPS; ED and ES images	Good correlation of regional wall shortening (r = 0.89) in patients after MI and in normal subjects
Rigo et al.[18]	GCBPS; ED and ES images	21 patients after MI; 12 of 13 with focal LV aneurysm detected with GCBPS; 9 of 9 with diffuse hypokinesia detected with GCBPS
Hopkins et al.[14]	GCBPS; ED and ES	35 patients after MI; 33 of 35 patients with abnormal contractility (diffuse or focal) detected with GCBPS
Friedman et al.[19]	GCBPS; ED and ES	Of 138 patients, 64 had aneurysm, 61 of which were detected with GCBPS; 72 of 74 normal subjects detected with GCBPS
Nichols et al.[24]	GCBPS	Of 36 patients with congestive heart failure and regional contractility abnormalities, 34 were detected with GCBPS
Froehlich et al.[25]	GCBPS	18 patients with angiographically resectable LV aneurysm; good correlation in 108 of 110 regional segmental contraction abnormalities; only 11 patients had a resectable aneurysm at operation
Botvinick et al.[26]	GCBPS; first pass	First case report describing scintigraphic appearance of false LV aneurysm; posterior in location with narrow neck, delayed filling of aneurysm on first pass study
Sweet et al.[27]	GCBPS; first pass	False LV aneurysm after coronary bypass graft surgery; posterior in position, delayed filling on first pass study
Winzelberg et al.[28]	GCBPS; thallium-201 perfusion scintiscan	Four patients with false LV aneurysm; frequent posterior position with discrete neck. Two patients with thallium defects in area of aneurysm

ED = end-diastolic; ES = end-systolic; GCBPS = gated cardiac blood pool scintiscan; LV = left ventricular; MI = myocardial infarction.

The physical examination, electrocardiogram and chest roentgenogram yield indirect and often inaccurate information regarding the presence and location of a left ventricular aneurysm.[3,14] Whereas early studies indicated the accuracy of cardiac cinefluoroscopy for the identification of aneurysm,[15,16] recent observations by Sos et al.[17] in 113 patients who had both cinefluoroscopy and contrast left ventriculography indicated that cinefluoroscopy was grossly inaccurate for detection and localization of left ventricular aneurysm and should not be routinely performed.[17] The gold standard for detection of left ventricular aneurysm has been contrast left ventriculography, but this procedure is both costly and invasive and is thus not well suited as a screening technique.

The widespread application of noninvasive radionuclide techniques,[14,18,19] including gated cardiac blood pool scintigraphy, thallium-201 myocardial perfusion scintigraphy and technetium-99m pyrophosphate myocardial scintigraphy, has provided accurate screening methods to identify patients with left ventricular aneurysm.

Gated Cardiac Blood Pool Scintigraphy*

Since its introduction in the early 1970s, gated cardiac blood pool scintigraphy has provided accurate noninvasive assessment of both regional and global myocardial function. Although the early images had suboptimal resolution and consisted of only end-systolic and end-diastolic images, the gated scan was nonetheless able to detect aneurysm of the left ventricle. Technologic improvements have allowed the gated blood pool scan to provide accurate assessment of both regional and global myocardial function at multiple points during systole and diastole. Improved intrinsic gamma camera resolution and data acquisition by computer systems have permitted a detailed assessment of the timing and extent of regional wall motion.

Technique and analysis of images: The techniques for blood pool labeling and correct imaging of the cardiac blood pool have been well described.[20–22] To evaluate patients for possible aneurysm, images should be obtained in at least three views: (1) anterior, (2) 45° left anterior oblique (to optimize imaging of the interventricular septum), and (3) 30° left posterior oblique. For optimal interpretation of the images the data should be displayed as a "continuous loop" movie with speed varying from stop motion to rates faster than real time. Evaluation of global left ventricular function and determination of the left ventricular ejection fraction is performed using the counts/volume approach.

Regional wall motion can also be accurately assessed from the gated blood pool scan and characterized as normal (greater than 20 percent shortening of a short axis diameter), hypokinesia (less than 20 percent but greater than 0 percent shortening) and akinesia/dyskinesia (0 percent or less shortening). The anterior view is best suited for evaluation of the apical, anterior and anterolateral walls of the left ventricle with the septum, apicoinferior and posterior walls being best seen in the left anterior oblique view. Inferior and basal wall motion is best evaluated in the left posterior oblique projection. Right ventricular function is best evaluated from the anterior and 45° left anterior oblique projections. Okada et al.[23] recently compared inter- and intraobserver variability in assessing regional wall motion abnormalities from gated cardiac blood pool scans as compared with contrast left ventriculograms and found a good correlation between both methods. Many investigators have documented a good correlation between gated blood pool scintigraphy and contrast left ventriculography in the evolution of left ventricular aneurysm (see Table I).

* All work performed with equilibrium blood pool scintigraphy can also be performed with first pass transit studies.

Comparison with contrast angiography: Zaret et al.,[21] using end-systolic and end-diastolic images, were the first to compare gated cardiac blood pool scintigraphy with contrast left ventriculography in both normal patients and patients with myocardial infarction and found a correlation coefficient of more than 0.89 for regional myocardial wall shortening. In a subsequent study by Rigo et al.[18] in 22 patients with myocardial infarction, contrast left ventriculograms revealed localized ventricular aneurysm in 13 patients and diffuse left ventricular hypokinesia in 9. Scintigraphy identified diffuse hypokinesia in all 9 patients and localized left ventricular aneurysm in 12 of the 13 patients. In one patient with a calcified left ventricular aneurysm filled with clot the gated cardiac blood pool scan showed an area of akinesia that corresponded to that seen in the contrast left ventriculogram, but the aneurysm was not seen. This was the first study that revealed that the biplane gated cardiac blood pool scan was useful in differentiating patients with localized left ventricular aneurysm from those with diffuse hypokinesia (Fig. 1 and 2).

Hopkins et al.[14] studied 35 patients after myocardial infarction with multiple symptoms including angina, dyspnea and congestive heart failure and compared results using static gated cardiac blood pool scans, computer assisted radionuclide cineangiography and contrast left ventriculography. The ventriculograms showed left ventricular aneurysm, as defined by segmental areas of akinesia or dyskinesia, in 18 patients and diffuse hypokinesia in 17 patients. Ten of the 18 patients with aneurysm had a dyskinetic segment whereas the remainder had an akinetic segment. Contrast left ventriculography confirmed the asynergy seen in static gated scans in 33 of the 35 patients. The computer-assisted radionuclide cineangiograms provided better images for qualitative assessment of wall motion abnormalities.

Accuracy of gated pool scans: More recently, Friedman et al.,[19] using the end-diastolic and end-systolic images from gated cardiac blood pool scans, evaluated 138 patients who also had contrast left ventriculography. Many of these patients also underwent surgery to confirm the diagnosis. The criterion for left ventricular aneurysm was an area of dyskinesia with regional systolic expansion. Contrast ventriculography showed 64 aneurysms (41 of 64 were confirmed at operation; 23 were not operated on). The distribution of the aneurysms was as follows: 29 anteroapical, 25 apical, 6 anterior, 3 posterobasal and 1 inferior. Sixty-one of the 64 aneurysms were identified on the gated scan. There were three false negative gated studies; a unidentified posterobasal aneurysm in two patients and an anterior wall aneurysm in one. The two posterobasal aneurysms appeared entirely normal on scanning. A clot was present in the anterior wall aneurysm making it undetectable in the gated study. The gated scan was negative in 72 of 74 patients in whom no aneurysm was found on contrast ventriculography (the negative findings were confirmed at operation in 35 of the 74; 39 patients were not operated on). There were two false positive scans, one falsely indicating an inferior wall aneurysm and one an aneurysm in the anterior wall. The overall accuracy of the gated scan for detecting aneurysms was 96 percent in relation to the contrast left ventriculogram. This high reliability of the gated scan to detect aneurysm may be partially related to the apical and anterior position of most of the aneurysms. These areas are particularly well seen in the gated scan with little interference from overlying structures. Thus the overall accuracy may not be as great with aneurysms located inferiorly or posteriorly.

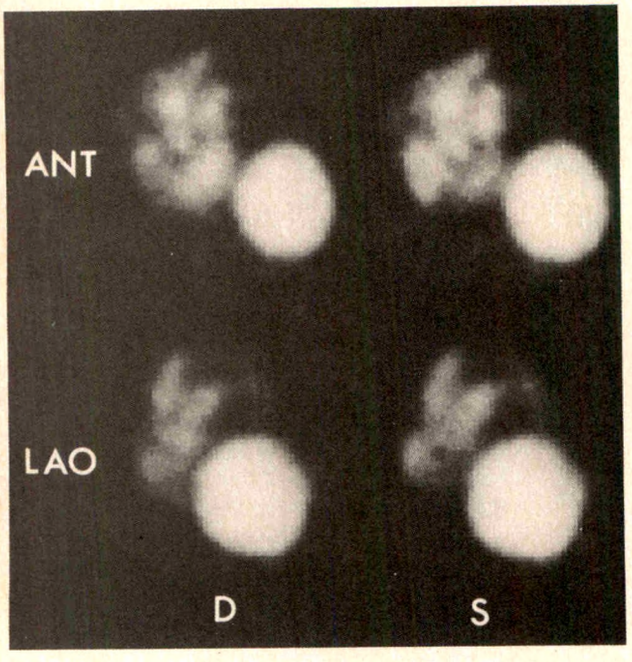


FIGURE 1. Anterior (ANT) and left anterior oblique (LAO) gated cardiac blood pool scintiscans at end-diastole (D) and end-systole (S) in a patient with occlusion of an isolated left anterior descending artery. After infarction, congestive heart failure developed and a large true anterolateral aneurysm was identified on scan and confirmed with contrast left ventriculography.

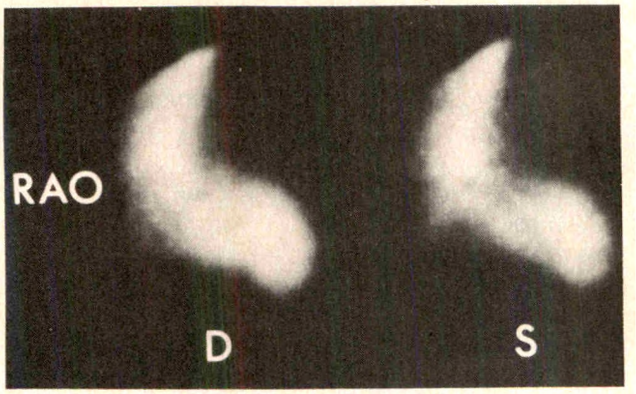


FIGURE 2. Right anterior oblique (RAO) gated first pass scintiscan at end-diastole (D) and end-systole (S) in a patient with a true left ventricular aneurysm confirmed with contrast ventriculography. There is relative preservation of contractility of the anterobasal and inferobasal left ventricular wall.

Nichols et al.[24] have also recently evaluated the gated scan in a large series of patients with congestive heart failure. In one subset of 36 patients who underwent both contrast left ventriculography and gated cardiac blood pool studies, the pattern of left ventricular dysfunction shown by the scan corresponded to the pattern in the left ventriculogram in 34.

In a prospective evaluation of the effects of surgery on left ventricular aneurysm, Froehlich et al.[25] showed a good correlation between contrast left ventriculography and gated blood pool scintigraphy in evaluating regional wall motion. They found agreement between abnormal versus normal motion in 108 of 110 myocardial segments evaluated in 18 patients who met angiographic criteria for resectable left ventricular aneurysm. In only two thirds of those patients with angiographically resectable aneurysm could resection be performed, and in 3 of the 18 patients no aneurysm was found.

False ventricular aneurysm: The gated cardiac blood pool scintiscan has also been utilized to detect

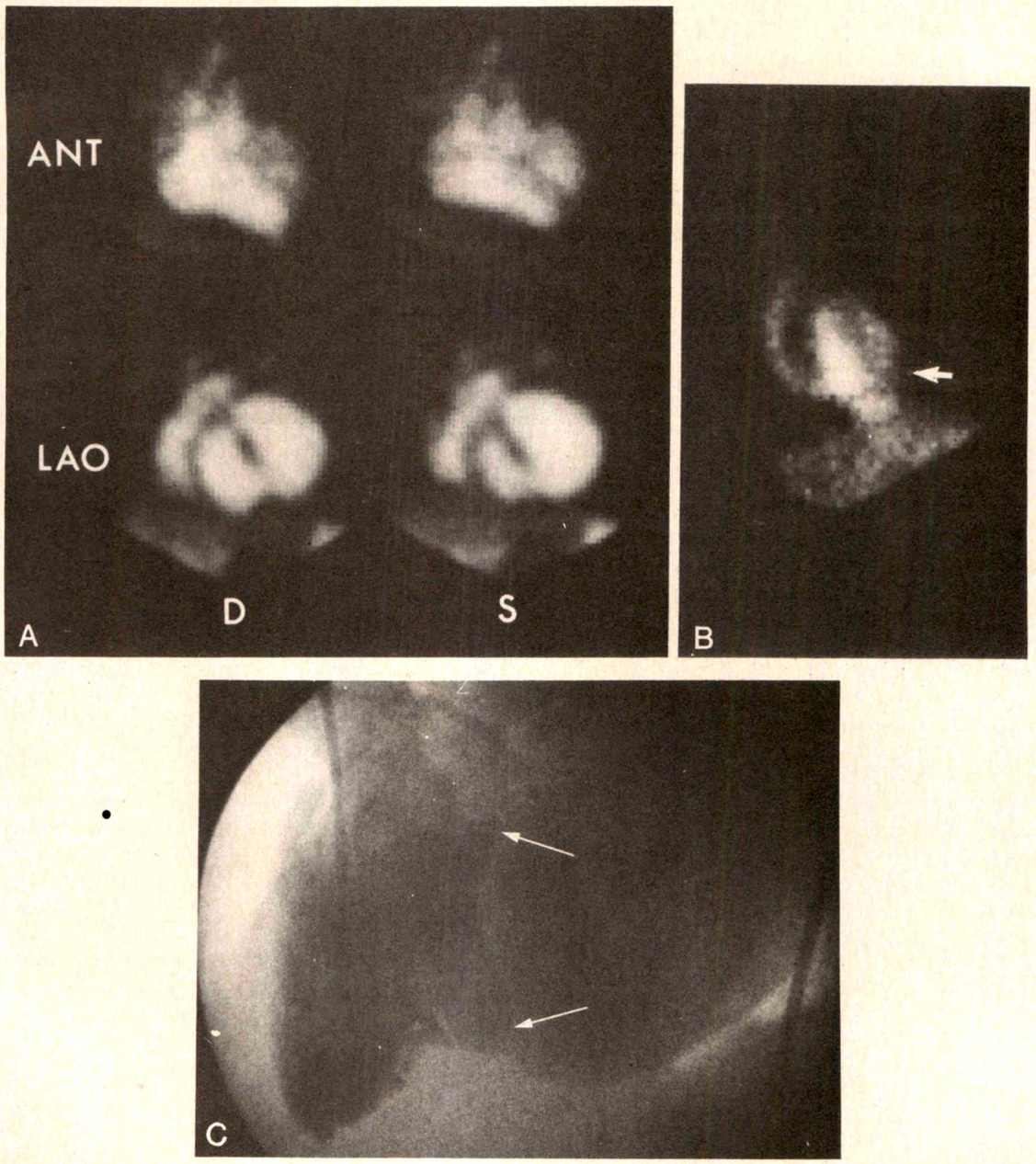


FIGURE 3. False left ventricular aneurysm. **A,** anterior (ANT) and left anterior oblique (LAO) gated cardiac blood pool scintiscan at end-diastole (D) and end-systole (S) in a diabetic patient with an occlusion of the left circumflex coronary artery. The cavity of a large false aneurysm is identified arising from the posterolateral left ventricular wall with a discrete neck connecting the true left ventricle to the aneurysm. **B,** thallium-201 perfusion scintiscan in the 45° left anterior oblique position demonstrating absent thallium uptake in the neck of the aneurysm (**white arrow**). **C,** contrast left ventriculogram in the left anterior oblique position demonstrating large posterior false aneurysm connected to the left ventricle by a narrow neck (**arrows**). (Reprinted by permission, from Winzelberg et al.[28])

false left ventricular aneurysms. Although such aneurysms occur much less frequently, they are important to identify because of a large incidence of fatal rupture. Botvinick et al.[25] first described the scintigraphic appearance of a false left ventricular aneurysm and stressed the posterior or lateral position and the discrete neck to the aneurysm (Fig. 3). Other investigators in single case reports have been able to distinguish false from true aneurysm in patients after infarction or in patients after cardiac surgery.[27] Winzelberg et al.[28] reported the findings in a series of false aneurysms that were studied with scintigraphic techniques. They confirmed the common posterior position of such aneurysms, which often have discrete necks.[28] Thallium-201 myocardial perfusion scintiscans were obtained in two of their patients. They suggested the following criteria for false left ventricular aneurysm in gated cardiac blood pool images: (1) a large paraventricular chamber, usually posterior in position, and (2) a narrow-necked connection between the chamber and ventricle. In thallium-201 myocardial perfusion images, the criterion is absent or greatly decreased activity in the myocardial wall in the connecting neck of the aneurysm.

Thallium-201 Myocardial Perfusion Scintigraphy and Technetium-99m Pyrophosphate Myocardial Scintigraphy

Thallium-201 perfusion scanning: This method has become an important adjunct in the noninvasive screening of patients with coronary artery disease.[28,29] Imaging of the myocardium after injection of thallium-201 at peak exercise reveals areas of scarring as regions of reduced uptake of tracer that are unchanged in images obtained 3 to 4 hours later. Zones of transiently ischemic myocardium may have diminished or absent tracer accumulation that returns to normal on delayed imaging. Studies in patients with a ventricular aneurysm have not been systematically carried out with thallium-201 imaging, but scarring due to aneurysm should appear no different from that not associated with aneurysm. Thallium imaging during exercise in conjunction with blood pool imaging may be helpful in identifying border zones of viable tissue adjacent to the left ventricular aneurysm.

Technetium-99m pyrophosphate imaging: Acutely infarcted myocardium can be imaged with technetium-99m pyrophosphate.[31,32] Deposition of tracer in acutely damaged tissue is related to the local accumulation of calcium ions in the area of infarcted myocardium. Recently, in some patients technetium-99m pyrophosphate scans have been "persistently positive" long after the acute episode of infarction. The deposition of technetium-99m–labeled pyrophosphate in a left ventricular aneurysm has been described as one cause of the persistently positive scan.[33] This finding may be related to microscopic or macroscopic dystrophic calcium deposition in the area of aneurysm formation or to ongoing ischemia along the margins of the aneurysm.

Ischemic cardiomyopathy: Gated cardiac blood pool imaging can serve as a major screening test to separate global from regional ventricular dysfunction and to separate false from true aneurysm in patients with congestive heart failure, malignant arrythmia or systemic emboli after myocardial infarction. With the gated scan, patients with ischemic cardiomyopathy in whom the entire left ventricle is poorly contracting can be separated from those with conditions that might surgically be corrected such as localized aneurysm formation or mitral regurgitation after myocardial infarction (papillary muscle dysfunction).[34] The findings of preserved left ventricular function (that is, ejection fraction greater than 35 percent), increased left ventricular end-diastolic volume and a large left atrium on gated scintigraphy after an infarction are good indirect evidence of mitral insufficiency.

Assessment of Aneurysm Resectability

Once a left ventricular aneurysm has been identified from the cardiac blood pool scintiscan, the question of resectability must be considered. Angiographic studies[1] have indicated two predictors of survival after left ventricular aneurysmectomy. The first is the extent of coronary artery disease and the second is the contractility of the nonaneurysmal portion of the left ventricle. Thus, Lee et al.,[1] using a modification of Feild's technique[34] to express the vigor of contraction of the normally contracting segment of myocardium, were able to calculate predicted ejection fraction of the ventricle composed of both abnormally and normally contracting segments. The amount by which the ejection fraction, calculated on the basis of normally contracting segments, differed from the actual ejection fraction was called the excess ejection fraction. Preoperative survival correlated with an excess fraction of more than +0.10. Application of this concept of the excess ejection fraction to the gated cardiac blood pool scintiscan should enhance the value of the gated scan in these patients and assist in selection of those who should undergo cardiac catheterization.

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M Mode and Two Dimensional Echocardiography in Mitral and Aortic Regurgitation: Pre- and Postoperative Evaluation of Volume Overload of the Left Ventricle

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Both M mode and two dimensional echocardiography are useful in determining the origin of mitral regurgitation. Two dimensional echocardiography appears to be superior to M mode echocardiography in the diagnosis of a flail leaflet, papillary muscle dysfunction and cleft mitral valve. It is possible to differentiate valvular causes from myocardial causes of regurgitation. Unfortunately, the severity of mitral regurgitation is difficult to quantify with either the M mode or the two dimensional technique. Echocardiography does allow differentiation of acute forms of mitral and aortic regurgitation from chronic volume overload of the left ventricle. Rupture of chordae tendineae is the most common cause of acute mitral regurgitation, and two dimensional echocardiography is 96 percent sensitive in its detection. Bacterial endocarditis, flail aortic valve and dissecting aneurysm as causes of acute aortic regurgitation can be detected with two dimensional echocardiography. Systolic left ventricular cavity dimension, percent fractional shortening and ejection fraction are important variables in predicting optimal time for surgery in patients with chronic aortic and mitral regurgitation. The noninvasive technique of echocardiography may be especially useful in decision making in the asymptomatic patient.

The two most common clinical entities associated with volume overload of the left ventricle are mitral regurgitation and aortic regurgitation. The clinical and hemodynamic responses to acute mitral and aortic regurgitation are totally different from those in the chronic situation. It is therefore incumbent on the clinician to recognize severe acute mitral and aortic regurgitation because of their devastating hemodynamic consequences. In this review we describe the echocardiographic findings in mitral and aortic regurgitation, with particular stress on acute regurgitation. In addition, we discuss the value of echocardiography in determining the optimal time for valve replacement in chronic mitral and aortic regurgitation.

Mitral Regurgitation

Mitral regurgitation is a syndrome rather than a specific disease entity. Mitral valve competence is dependent on normal and coordinated function of the mitral valve anulus, mitral valve leaflets, chordae tendineae, papillary muscles and left ventricular myocardium.[1] Dysfunction of any one or a combination of structures may lead to mitral valve regurgitation.

Table I lists the causes of the murmur of mitral regurgitation in a series of 289 patients (constituting approximately 20 percent of all patients undergoing two dimensional echocardiographic studies in our laboratory) with a clinical diagnosis of mitral regurgitation. Each patient had an apical holosystolic or late systolic murmur that was confirmed with phonocardiography. In some instances, amyl nitrite was given to a patient in order to differentiate between a regurgitant and an ejection-type murmur.

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TABLE I

Etiology of Murmur of Mitral Regurgitation in 289 Consecutive Patients

	Patients	
	n	%
Rheumatic heart disease	80	28
Prolapse	70	24
Papillary muscle dysfunction	49	17
Flail mitral leaflet	44	15
Mitral anular calcification	15	5
Unknown	12	4
Cleft anterior mitral leaflet	9	3
Idiopathic hypertrophic subaortic stenosis	5	2
Endocarditis	3	1
Left atrial myxoma	2	1
Total	289	100%

Rheumatic heart disease: *The M mode echocardiographic features of rheumatic mitral regurgitation include* (1) a normal to slightly decreased amplitude of mitral valve motion as a result of some degree of valve fibrosis; (2) a varying E-F slope; (3) thickened mitral leaflets; (4) parallel motion of both anterior and posterior leaflets during diastole; (5) pattern of volume overload of the left ventricle characterized by an enlarged left ventricle and hyperdynamic motion of the septum and posterior wall; and (6) an enlarged left atrium. On occasion some of these findings are indistinguishable from those of true mitral stenosis. In a few patients, a greatly reduced amplitude of motion and a flat E-F slope can be recorded that are similar to the findings in patients with mitral stenosis. In patients with mixed mitral stenosis and insufficiency, a "ski slope" appearance has been described. This consists of a brisk downward E-F slope initially and then a more gradual, flatter diastolic slope during the mid and latter portions of diastole. Systolic motion is usually normal, a feature that is helpful in distinguishing rheumatic mitral regurgitation from mitral valve prolapse.

The two dimensional echocardiographic features include: (1) thickened mitral valve leaflets; (2) an obtuse angular bend of the anterior mitral leaflet in diastole, particularly apparent in the parasternal long axis view (Fig. 1A); (3) a relatively stationary posterior mitral leaflet in the parasternal long axis view; (4) an enlarged left ventricle and left atrium with hyperdynamic motion of the septum and posterior wall; and (5) failure of closure of small areas of either the medial or lateral aspect of the mitral valve in parasternal short axis views[2] in mild mitral regurgitation or failure of the mitral valve to close in the center in severe regurgitation (Fig. 1B). Eighty of our 289 patients fulfilled the two dimensional echocardiographic criteria for the diagnosis of rheumatic mitral regurgitation. Fifty-two of these patients underwent cardiac catheterization, which confirmed the diagnosis of mitral regurgitation. Fifty-six patients had mixed mitral stenosis and regurgitation; 15 of these underwent mitral valve replacement. Twenty-four patients had pure mitral regurgitation, and 12 of these patients underwent mitral valve replacement. Patients with pure regurgitation generally had a larger diastolic mitral valve area measurement (usually 3.0 cm^2 or greater) in the parasternal short axis view compared with patients with mixed mitral stenosis and insufficiency, who had a reduced mitral valve orifice generally measuring less than 2.0 cm^2.[3]

Mitral valve prolapse: The next major group in our series includes 70 patients with mitral valve prolapse, 21 of whom underwent cardiac catheterization. The catheterization findings confirmed the presence of prolapse with varying severity of mitral regurgitation. Eight patients had significant mitral regurgitation and required valve replacement. The two dimensional echocardiographic features of prolapse will be described as a separate entity elsewhere in this Symposium.[4] It is usually possible to distinguish between rheumatic mitral regurgitation and mitral valve prolapse with two dimensional echocardiography. In rheumatic mitral regurgitation, normal coaptation of the mitral leaflets during systole is preserved, whereas in mitral valve prolapse an abrupt posterior and superior buckling of one or both leaflets into the left atrium is seen in the parasternal long axis views.

Papillary muscle dysfunction: Included in this group are 49 patients, 23 of whom underwent cardiac catheterization. In those patients who underwent left ventriculography, diffuse or segmental angiographic abnormalities of left ventricular wall motion and varying grades of severity of mitral regurgitation were evident. In the entire group, 38 patients had clinical and electrocardiographic evidence of coronary artery disease and 11 had congestive cardiomyopathy. Papillary muscle motion and thickening are best assessed in the pasternal short axis view.[3] Two dimensional echocardiography reveals diffuse or segmental abnormalities of left ventricular wall motion adjacent to and involving one or both of the papillary muscles (Fig. 2). These abnormalities consist of either akinesia, hypokinesia, dyskinesia or absence of regional wall thickening. Minimal counterclockwise left ventricular rotation during systole occurs in both normal subjects and patients with heart disease.[5] This finding should be taken into account when evaluating the frame by frame motion of the papillary muscles. In the parasternal long axis or four chamber apical view, the systolic coaptation point is inferiorly displaced into the body of the left ventricle, presumably as a result of the fibrosed and scarred papillary muscle.[6]

Flail mitral valve leaflet: Rupture of the chordae tendineae is responsible for the acute mitral regurgitation of most patients. The condition can occur as an isolated spontaneous phenomenon in an otherwise normal heart or as a complication of mitral valve prolapse, rheumatic mitral disease, bacterial endocarditis or atrial myxoma.[7] Forty-four patients are included in this group. Thirty-eight of these patients underwent cardiac catheterization, and mitral valve replacement was performed in 33. Twenty-three had anterior and 21 had posterior mitral leaflet involvement.

In the parasternal long axis view of the cross-sectional echocardiogram, there is systolic motion of the tip of the anterior or posterior mitral leaflet into the left

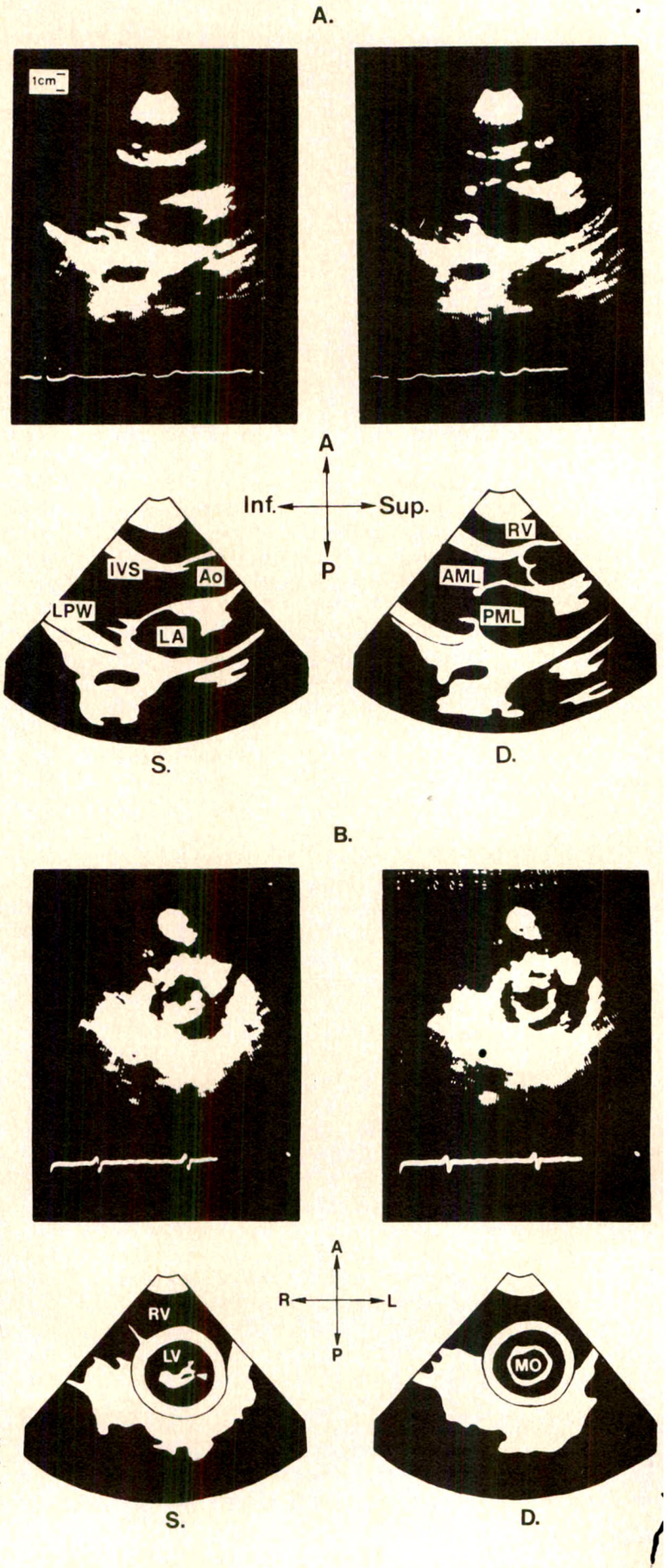


FIGURE 1. Two dimensional echocardiograms in rheumatic mitral regurgitation. **A**, parasternal long axis views. **Left panel** demonstrates the mitral valve and left ventricle during systole (S). Both leaflets and chordal structures are minimally thickened. **Right** panel obtained during diastole (D.) demonstrates the typical obtuse angle bend of the anterior mitral leaflet (AML). **B**, parasternal short axis views in a different patient. **Left panel** demonstrates thickened mitral valve leaflets and failure of the valve to close in the central area. **Right panel** obtained in cross section during diastole demonstrates a mitral valve area measuring 3.0 cm^2. A = anterior; Ao = aorta; Inf. = inferior; IVS = interventricular septum; L = left; LA = left atrium; LPW = left ventricular posterior wall; LV = left ventricle; MO = mitral valve orifice; P = posterior; PML = posterior mitral leaflet; R = right; RV = right ventricle; Sup. = superior.

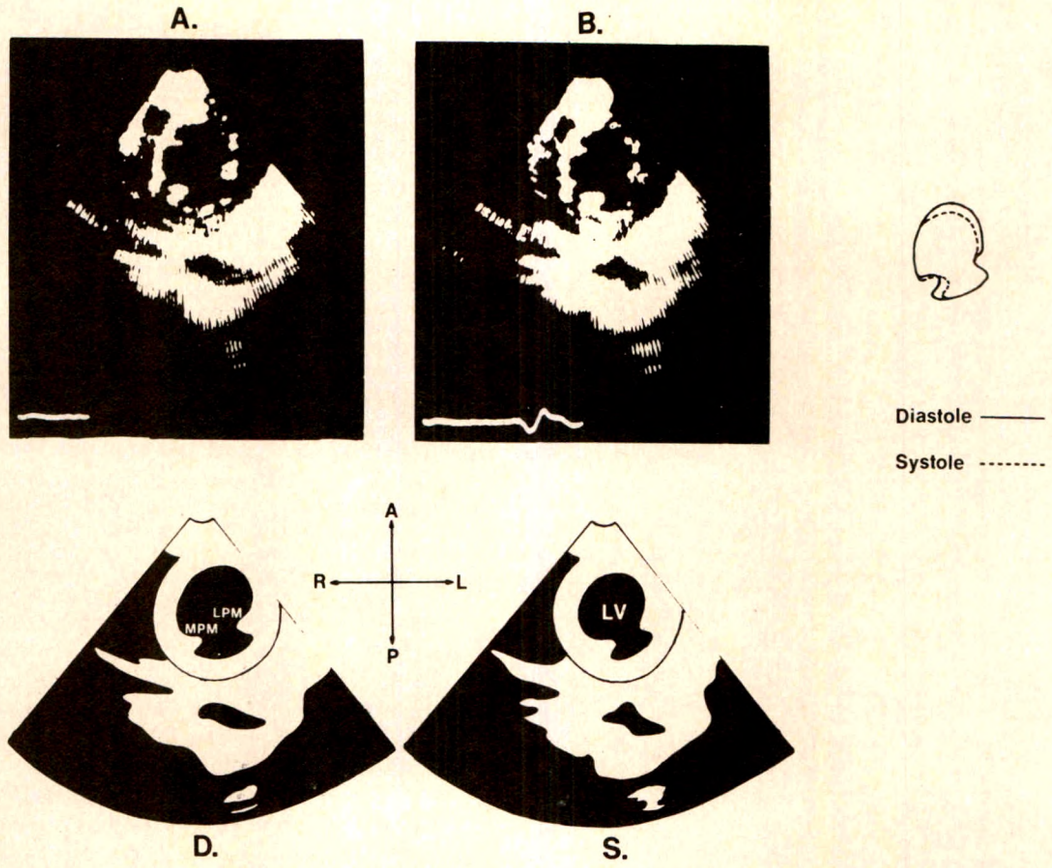


FIGURE 2. Two dimensional echocardiogram in the parasternal short axis view at the level of the papillary muscle in a patient with mitral insufficiency secondary to papillary muscle dysfunction and coronary artery disease. End-diastolic (D.) and end-systolic (S.) frames are accompanied on the **right** by a line drawing of superimposed diastolic (**solid line**) and systolic (**dotted line**) endocardial surfaces. The anterolateral papillary muscle (LPM) is akinetic as is the lateral and inferior wall of the left ventricle (LV). The posteromedial papillary muscle (MPM) is minimally hypokinetic. The medial portion of the septum is akinetic, whereas the superior portion and the anterior wall of the left ventricle are hypokinetic.

atrium beyond the normal coapatation of the leaflets (Fig. 3).[8] Normal coaptation of the leaflets is not present. Recently, a "snake tongue" deformity has been described,[9] to denote a rapid, curling darting-like motion of a leaflet into the left atrium beyond the closure point. The differentiation between a flail leaflet and mitral valve prolapse is also apparent in Figure 3.

The classic M mode echocardiographic findings in flail mitral leaflet include systolic intracavitary left atrial echoes, systolic mitral valve flutter, coarse diastolic anterior leaflet flutter in a flail anterior leaflet and either paradoxical and chaotic posterior leaflet motion or early diastolic posterior leaflet flutter in a flail posterior leaflet. In a recent study, Mintz et al.[10] demonstrated that the sensitivity of M mode echocardiography is only 60 percent in diagnosing a flail leaflet. In addition, systolic mitral flutter and paradoxic posterior leaflet motion and systolic left atrial echoes are specific but insensitive for a flail leaflet.

The diagnostic sensitivity increases to 90 percent when two dimensional echocardiography is used.[10] However, the specificity of two dimensional echocardiography is only 84 percent. In the study of Mintz et al.,[10] 16 percent (3 of 19 patients) with significant mitral regurgitation and intact chordae tendineae had a false positive two dimensional study that suggested a flail leaflet. In one patient with severe mitral valve prolapse, asymmetrically elongated chordae tendineae allowed the tip of the anterior leaflet to prolapse beyond the posterior leaflet into the left atrium. Although the chordae were intact, the anterior leaflet was "functionally flail." The two other patients with a false positive study had rheumatic mitral regurgitation. In both, the chordae tendineae to the posterior leaflet were thickened and intact and those to the anterior leaflet were lax. During systole, the posterior leaflet remained in a fixed position and the tip of the anterior leaflet overshot the fixed posterior leaflet into the left atrium. It appears that in these patients, the valve was functionally flail as well. The importance of recognizing a flail leaflet is obvious. Generally, the patients have severe regurgitation and signs of heart failure with a normal or only slightly enlarged left atrium and hyperdynamic motion of the ventricular walls.

Mitral anular calcification: Fifteen patients with the typical M mode echocardiographic of mitral anular calcification findings are included in our series. A characteristic pattern of a dense band of echoes just

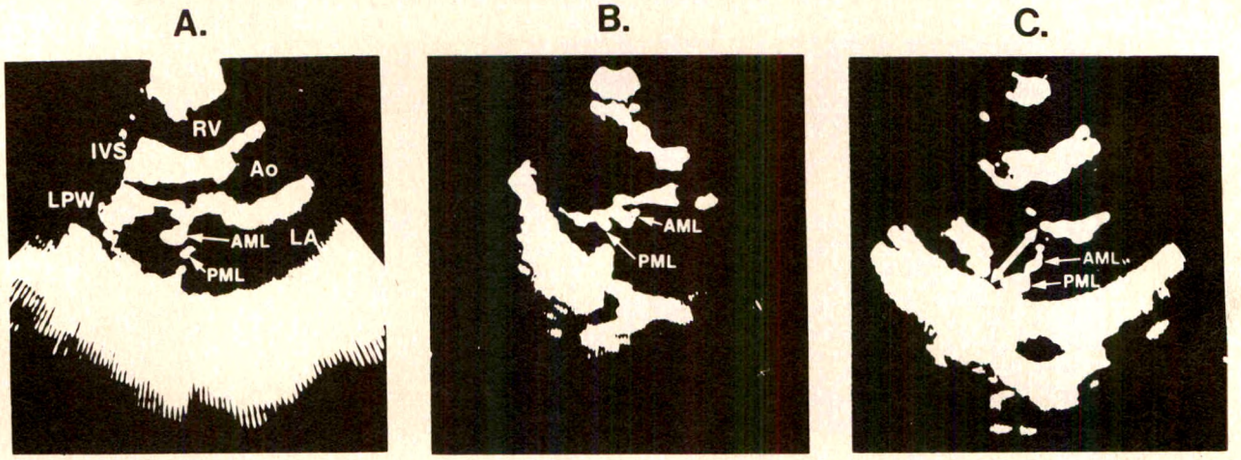


FIGURE 3. Flail mitral leaflet versus mitral valve prolapse. All panels were obtained in the parasternal long axis view during systole. In **A**, a flail posterior mitral leaflet (PML) is visualized with motion of the leaflet beyond the normal coaptation point into the left atrium (LA). **B** depicts a flail anterior leaflet (AML) with curling and bending of the tip of the anterior leaflet into the left atrium beyond the line of coaptation. **C** demonstrates mitral valve prolapse with both anterior and posterior leaflets arched superiorly during systole beyond the plane of the mitral anulus (**double-headed white arrow**). Ao = aorta; IVS = interventricular septum; LPW = left ventricular posterior wall; RV = right ventricle.

posterior to the mitral leaflet frequently obscuring the posterior leaflet and having systolic motion parallel to the left ventricular posterior wall is observed. These echoes extend from the atrioventricular junction into the body of the left ventricle. Other associated abnormalities may be present in patients with mitral anular calcification, and associated aortic valve sclerosis and conduction disturbances may be present.[6] Mitral anular calcification frequently occurs as a degenerative disorder in aged persons. It has been reported in patients with Marfan's syndrome, chronic renal failure, atherosclerosis and idiopathic hypertrophic subaortic stenosis.[6] A recent study[11] has suggested that the calcification actually occurs in the submitral area in the elderly patients. The majority of patients have posterior submitral calcification that is located in the angle between the posterior mitral leaflet and left ventricular posterior wall, rather than in the mitral anulus proper. Anterior submitral calcification is usually located anterior to the base of the anterior mitral leaflet.

The two dimensional echocardiographic features of mitral anular calcification include a dense crescent-shaped band of echoes between the posterior mitral leaflet and left ventricular posterior wall in the parasternal short axis view. For defining the extent of calcification, the parasternal long axis view or apical view may be more suitable (Fig. 4). It is unlikely that two dimensional echocardiography is more sensitive than M mode echocardiography in the diagnosis of mitral anular calcification.

Unknown cause: Twelve patients in our series, including six who underwent cardiac catheterization, had no apparent cause of the mitral regurgitation. The severity of regurgitation in this group ranged from 1 to 3+. All 12 had normal left ventricular wall motion, although 2 had associated significant coronary artery disease (greater than 50 percent narrowing).

Cleft mitral valve: The nine patients in our series with a left mitral valve all underwent cardiac catheterization. Four required surgical repair of an ostium primum atrial septal defect as well as repair of the cleft valve. The cleft mitral valve leaflet is not apparent with M mode techniques although, in patients who have an associated primum defect, a narrowed left ventricular outflow tract and prolonged diastolic apposition of the anterior mitral leaflet against the septum is evident. On two dimensional echocardiography, systolic mitral valve motion in patients with a cleft mitral valve is normal. However, in parasternal short axis views during diastole, the anterior leaflet of the mitral valve opens like a drawbridge into two distinct components. The posterior leaflet motion is normal.

Idiopathic hypertrophic subaortic stenosis: Five patients in our series had idiopathic hypertrophic subaortic stenosis; four of these underwent cardiac catheterization. In each patient, M mode and two dimensional echocardiography revealed asymmetric septal hypertrophy and systolic anterior motion of the mitral valve. The four patients who underwent cardiac catheterization had a left ventricular outflow gradient at rest or with provocation, and mitral regurgitation was found in all four. None of the five patients underwent surgery.

Mitral vegetation: Three patients had evidence of endocarditis; two patients underwent cardiac catheterization. None of the three had mitral valve prolapse, either clinically or on echocardiography or at cardiac catheterization. On two dimensional echocardiography, a large vegetation with increased echo density attached to the anterior mitral leaflet was apparent. None of these patients underwent surgery and all are being treated medically. It is not possible to differentiate between active and healed endocarditis with M mode or two dimensional echocardiography.

Left atrial myxoma: In the two patients with a left atrial myxoma, the M mode echocardiogram was compatible with the large prolapsing mass into the mitral valve. The two dimensional echocardiographic study in

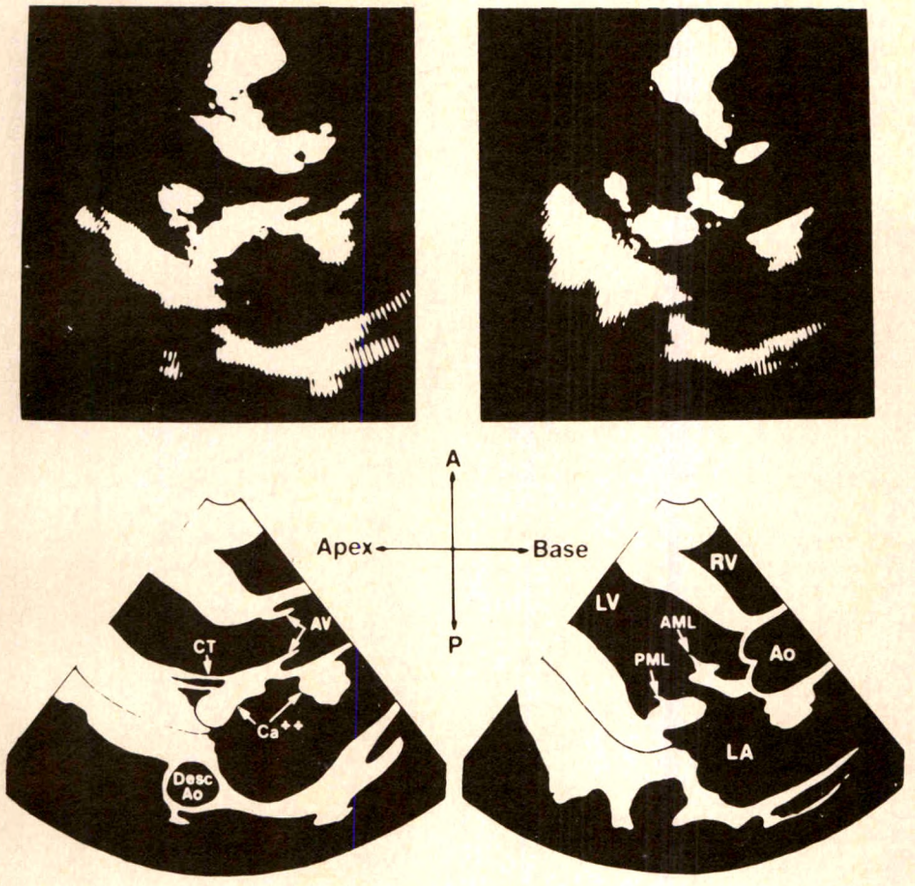


FIGURE 4. Two dimensional echocardiogram in a patient with severe mitral anular calcification obtained in the parasternal long axis views during systole (**left**) and diastole (**right**). Dense echoes are recorded in the post-mitral leaflet and submitral area and to a lesser extent in the area of the anterior mitral leaflet and posterior aortic wall. A = anterior; AML = anterior mitral leaflet; Ao = aorta; AV = aortic valve; Ca^{++} = calcium; CT = chordae tendineae; Desc = descending; LA = left atrium; LV = left ventricle; P = posterior; PML = posterior mitral leaflet; RV = right ventricle.

both instances demonstrated a large echo-dense mass moving from the left atrium into the left ventricular inflow tract during late diastole. In one patient, surgery confirmed the presence of a large tumor. The other patient died just before operation. In both instances, the patients presented with a murmur of mitral regurgitation without any evidence of a mid diastolic rumble or tumor plop.

Mitral regurgitation and surgery: Patients with severe mitral regurgitation (both acute and chronic varieties) requiring valve replacement can be recognized with two dimensional echocardiography; however, the severity of the condition is difficult to quantify.[10] The most common indications for mitral valve replacement are rheumatic heart disease, rupture of the mitral chordae tendineae, postinfarction rupture of the papillary muscle, intractable infective endocarditis, floppy mitral valve and malfunction of a prosthetic valve.[12] Less common conditions that may require mitral valve replacement for regurgitation are transposition of the great arteries, partial atrioventricular canal, endocardial fibroelastosis, shortened or redundant posterior leaflet, accessory orifice, anomalous mitral arcade, isolated cleft anterior mitral leaflet or papillary muscle infarction. In addition, rarities such as Marfan's syndrome, with or without calcified anulus and elongated chordae tendineae, hypertrophic cardiomyopathy, osteogenesis imperfecta, carcinoid heart disease and methysergide-induced heart disease may require mitral valve replacement. In our institution, ruptured chordae tendineae accounted for 58 percent of patients requiring mitral valve replacement for *pure* mitral regurgitation.[9] This was followed by rheumatic mitral regurgitation without stenosis in 20 percent, papillary muscle fibrosis in 9 percent, myxomatous leaflet degeneration without ruptured chordae in 6.5 percent and isolated cleft mitral leaflet in 6.5 percent.

Aortic Insufficiency

In early reports,[7] rheumatic or syphilitic involvement accounted for the majority of patients with chronic aortic insufficiency. With the decline in the incidence of these two diseases, aortic insufficiency has become a clinical spectrum comprising multiple causes. Bicuspid aortic valve, ankylosing spondylitis, myxomatous degeneration of the aortic leaflets, trauma, osteogenesis imperfecta, rheumatoid arthritis, Reiter's syndrome, Ehlers-Danlos syndrome, dissection of the aorta, Hurler's syndrome and ventricular septal defect may be associated with aortic insufficiency.[7] On rare occasions, a murmur of aortic insufficiency may be associated with severe anemia, chronic renal failure and severe hypertension.

Acute aortic insufficiency must be differentiated from chronic aortic insufficiency. The causes of acute severe regurgitation include infective endocarditis,

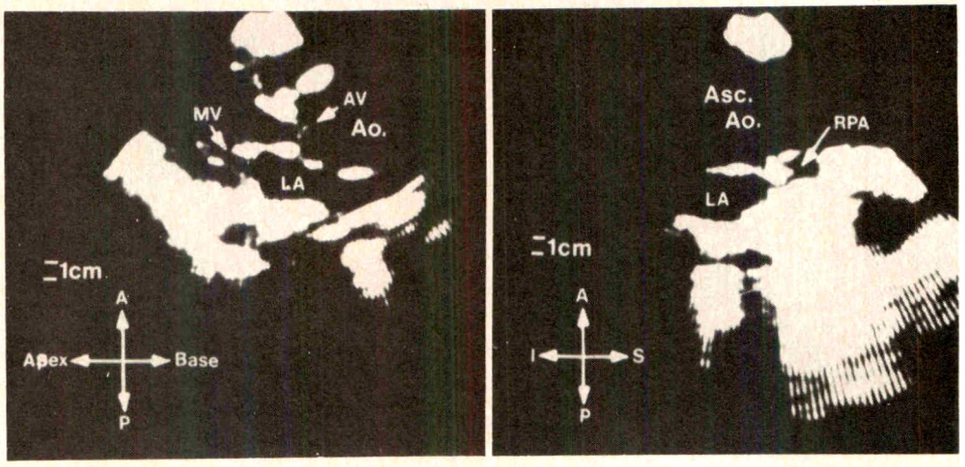


FIGURE 5. Two dimensional echocardiogram in saccular aneurysm of ascending aorta obtained in the parasternal long axis view. **Left,** marked saccular dilatation of the ascending aorta with an enlarged aortic (Ao.) root anulus is demonstrated in a patient with aortic insufficiency. The aortic leaflets in this patient are normal. **Right,** aortic root in the parasternal long axis view in the second right intercostal space. The markedly enlarged ascending aorta (Asc. Ao.) anteriorly, with a normal-sized right pulmonary artery (RPA), and the left atrium (LA) posteriorly are demonstrated. The aortic root measures 5.5 cm. A = anterior; AV = aortic valve, I = inferior; P = posterior; MV = mitral valve; S = superior.

dissecting aneurysm, traumatic rupture or prolapse of an aortic leaflet and myxomatous degeneration.[13]

In chronic aortic regurgitation, gradually increasing preload permits the left ventricle to function as an effective low compliance pump with little or no increase in filling pressure. Left ventricular mass increases mainly because of an increase in left ventricular internal dimension at end-diastole with relatively little increase in wall thickness. With dynamic exercise, the peripheral vascular resistance decreases, diastole shortens as a result of increased heart rate and regurgitant fraction per beat decreases; thus, an increase in cardiac output can be achieved. Although end-diastolic volume is increased because of regurgitation of blood into the ventricle, it does not increase further with exercise.

In acute severe aortic insufficiency, the adaptative powers of the left ventricle are restrained. End-diastolic pressure increases dramatically in reaction to the acute increase in volume because of the constraints imposed on filling by the noncompliant left ventricle and, to a lesser extent, the pericardium.[13] The effective stroke volume is decreased and there is a compensatory tachycardia. In addition, the peripheral vascular resistance is increased as a means of maintaining systemic arterial pressure. The dramatic increase in left ventricular end-diastolic pressure exceeds an elevated left atrial pressure and is responsible for premature mitral valve closure seen in some patients with severe acute regurgitation.[14]

M mode echocardiography: The characteristic M mode echocardiographic finding of aortic insufficiency is diastolic fluttering of the anterior mitral leaflet[15] and, to a lesser extent, of the posterior mitral leaflet. High flow states such as left to right shunt and chronic anemia may be associated with fluttering as well. The presence or absence of diastolic fluttering of the mitral valve is not related to the degree of aortic regurgitation. In patients with associated mitral stenosis and thickened leaflets, fluttering of the mitral valve may not be readily detected. In such patients, fluttering of the ventricular septum should be looked for because it has been reported to occur in patients with aortic insufficiency.[16] These high frequency vibrations are not readily appreciated with two dimensional echocardiography.

Other M mode echocardiographic findings include left ventricular dilatation, hyperdynamic septal and left ventricular wall motion and, on occasion, an increase in aortic root diameter. In patients with a very high end-diastolic pressure, such as that observed in acute aortic insufficiency, premature mitral valve closure and less commonly premature aortic valve opening have been reported.[17] Diastolic fluttering of the aortic valve has been reported in patients with flail aortic leaflets secondary to bacterial endocarditis and myxomatous degeneration.[15] Thus, M mode echocardiography may be more sensitive than two dimensional echocardiography in predicting hemodynamic changes in patients with aortic insufficiency.

Two dimensional echocardiography: More precise information can be obtained with two dimensional echocardiography with regard to etiologic diagnosis. Aortic root lesions as a cause of aortic insufficiency can be separated from valvular causes with two dimensional echocardiography. Saccular aneurysms of the ascending aorta have been visualized with two dimensional echocardiography[18] (Fig. 5). In addition, the spiral aortic tear separating the true lumen from the false lumen in patients with aortic dissection has been observed.[18] In patients with aortic valve endocarditis, valve destruction may produce a flail aortic valve leaflet. Both M mode and two dimensional echocardiography may not visualize a distinct vegetative growth, although two dimensional echocardiography may detect a flail aortic leaflet more readily than M mode echocardiography[19] (Fig. 6).

Echocardiography in Determining Optimal Time for Surgery in Chronic Volume Overloading of the Left Ventricle

Chronic aortic insufficiency: It has been reported[20] that if surgery for patients with aortic regurgitation is

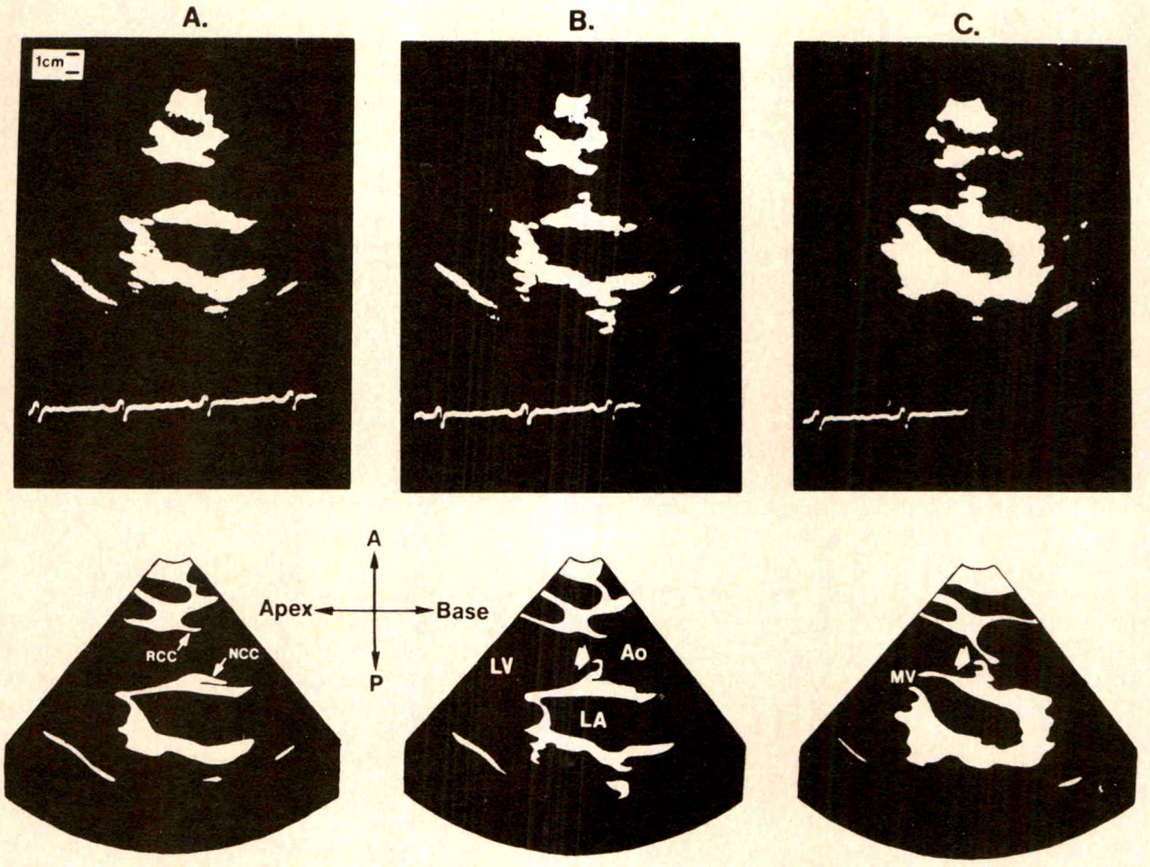


FIGURE 6. Two dimensional echocardiograms obtained in the parasternal long axis view depicting the valve motion in a flail aortic valve. **A**, shows the normal aortic cusps; the right (RCC) and noncoronary cusps (NCC) open during systole with the leaflets opposing the respective walls of the aorta. **B**, shows the aortic (Ao) leaflets in early diastole with the right coronary cusp in the closing position and the noncoronary cusp (**arrow**) beginning to prolapse into the left ventricular (LV) outflow tract. **C**, shows the leaflets during later diastole with normal closure of the right coronary cusp and eversion and prolapse of the noncoronary cusp into the outflow tract (**arrow**). The flail aortic leaflet resulted from bacterial endocarditis, but no vegetation was demonstrated. A = anterior; LA = left atrium; MV = mitral valve; P = posterior.

deferred until significant symptoms develop, approximately 50 percent of patients surviving the procedure die within 5 years, most from congestive heart failure secondary to irreversible myocardial damage.

A group of 50 patients who underwent aortic valve replacement for isolated symptomatic aortic regurgitation were studied prospectively. There were three operative deaths (6 percent), and seven patients died of congestive heart failure in a follow-up period ranging from 5 to 37 months after surgery. There were no significant preoperative hemodynamic or electrocardiographic predictors of late death from congestive heart failure. M mode echocardiographic indexes of systolic function (ejection fraction, fractional shortening and end-systolic dimension) were accurate predictors of late congestive heart failure. Of 17 patients with a preoperative left ventricular end-systolic dimension greater than 55 mm, 47 percent died either at operation or of postoperative congestive heart failure. In 29 percent of the patients who are alive, impaired left ventricular systolic function is still present postoperatively, whereas only 24 percent have normal postoperative systolic function. In contrast, of 33 patients with a preoperative end-systolic dimension less than 55 mm, 85 percent are still alive, and only 1 of 5 deaths was due to congestive heart failure.

In order to test the hypothesis that patients should be operated upon once systolic dysfunction is documented, another group of 37 patients with asymptomatic aortic regurgitation were studied prospectively.[21] The mean follow-up period was 34 months. Fourteen patients (38 percent) subsequently manifested symptoms that required operation and 23 (62 percent) remained asymptomatic during the follow-up period. Four (80 percent) of five patients with a preoperative end-systolic dimension greater than 55 mm subsequently had symptoms and required surgery. Of the 20 patients whose initial end-systolic dimension was 50 mm or less, only 4 (20 percent) had symptoms that required operation and none died during the follow-up period.

Exercise studies may also be helpful in predicting timing of operation. Patients with impaired systolic function on echocardiography but with good treadmill exercise capacity have reversible myocardial disease; systolic function returns to normal after operation and death from congestive heart failure is rare. Patients with impaired systolic function on M mode echocardiography

who exercised poorly on the treadmill have a large incidence of left ventricular dysfunction and a propensity for the development of congestive heart failure and death. It thus appears that asymptomatic patients with aortic regurgitation and a left ventricular end-systolic dimension less than 50 mm appear to be at low risk for the development of congestive heart failure and can be safely followed up with yearly M mode echocardiograms. Patients with an end-systolic dimension between 50 and 54 mm who are asymptomatic should be carefully followed up with serial echocardiograms every 4 to 6 months. On the basis of these observations, Henry et al.[21] are recommending surgery in patients with asymptomatic aortic regurgitation who have an end-systolic dimensions of 55 mm or greater.

Chronic mitral regurgitation: In the presence of chronic volume overload, left ventricular function represents a complex interaction between myocardial contractile state, fiber length and afterload. In chronic mitral regurgitation, afterload is affected by a low impedance system occurring as a result of a large distended left atrium. An unexpected worsening of left ventricular function may occur early after mitral valve replacement.[22] On the basis of the M mode preoperative echocardiographic findings, Schuler et al.[22] were able to differentiate between two subgroups of patients with mitral regurgitation. In patients with mitral regurgi tation who have moderate left ventricular dilatation and a normal ejection fraction preoperatively, regression o myocardial hypertrophy and only minimal reductio of left ventricular percent shortening may occur afte mitral valve replacement. In contrast, in patients wit mitral regurgitation with significant left ventricula dilatation (end-diastolic and end-systolic diameter 7.(and 5.0 cm, respectively) and a low normal or decreasec ejection fraction preoperatively, further depression o left ventricular ejection fraction with persistent cavity dilatation and wall hypertrophy were observed afte mitral valve replacement. In the latter group it appear that left ventricular shortening has become partially dependent on systolic afterload reduction through a lo impedance leak.

Thus M mode echocardiography provides accurate prognostic information with regard to reversible o irreversible left ventricular function in patients wit chronic volume of the left ventricle. Whether two di mensional echocardiography, by providing more accu rate overall left ventricular chamber dimensions and ejection fraction determination, will enhance the ability of noninvasive techniques to determine operability i patients with a volume overloaded ventricle remains t be seen.

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Current Status of Radionuclide Imaging in Valvular Heart Disease

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In valvular heart disease, there is a different radionuclide angiographic pattern in each of three left-sided valve abnormalities: pressure overload (aortic stenosis), volume overload (aortic or mitral regurgitation) and inflow obstruction (mitral stenosis). In *pressure overload,* the left ventricle is usually normal in size or minimally dilated. The ejection fraction may be normal, increased or decreased. In *volume overload,* there is left ventricular dilatation with a normal or reduced ejection fraction at rest. Scans may be performed during exercise to unmask abnormalities of ventricular function not evident at rest. In *inflow obstruction,* left ventricular function is usually normal but may be depressed. Right ventricular function may be abnormal secondary to pulmonary hypertension.

Radionuclide angiography in valvular heart disease evaluates the impact of the valve abnormality on cardiac chamber size and function, which is useful in managing the patient, in determining the prognosis and in evaluating the success of valve surgery. Thallium-201 imaging evaluates regional myocardial blood flow and cell integrity and can be used to assess associated coronary artery disease.

Patients with valvular heart disease may have heart failure on the basis of mechanical factors or depression of ventricular contractile function.[1–4] Differentiation of the contribution of each of these factors to cardiac insufficiency is important in both management and prognosis.[5,6] Radionuclide methods are helpful in assessing this clinical problem.[7] Radionuclide angiography can define the impact of the valvular abnormality on cardiac chamber size and function, whereas thallium-201 myocardial imaging may be helpful in detecting and evaluating associated coronary artery disease. Assessment of ventricular function constitutes the single most important use of radionuclide imaging in valvular heart disease. Preoperative studies are useful in determining when is the appropriate time to intervene surgically and when a patient may be a poor operative risk.[8–10] These approaches have also helped to define results to be anticipated postoperatively.

Ejection Fraction in Valvular Heart Disease

Ejection fraction is one of the most easily measured and valuable indexes of ventricular function.[11–16] The normal ejection fraction range depends on the method by which it is obtained.[17] A reduction in ejection fraction correlates with the presence of clinical heart failure[18] and generally implies a worse clinical course.[6,19] However, the ejection fraction has three important diagnostic limitations[20]: (1) dependence on "extrinsic" determinants of ejection; (2) tendency to normalize with compensatory mechanisms; and (3) lack of correlation with heart failure.

The first limitation is that ejection fraction is a complex function of both "intrinsic" myocardial contractile performance and four "extrinsic" determinants of stroke volume. These extrinsic factors include heart rate, afterload (systolic wall stress), preload (end-diastolic volume) and factors that influence the inotropic state.[4,12,15,21] Ejection fraction tends to be lower at higher heart rates;[22–25] it decreases with increasing afterload;[23,26–30] it increases with increasing preload;[23,28,30–33] and it increases with increased inotropic stimulation.[30] The influence of these

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"extrinsic" factors becomes a particular problem in valvular heart disease because of the occurrence of large alterations in preload or afterload or both.[34] Therefore, the ejection fraction may be misleading, and direct inferences from this value about myocardial function should be made with caution.[27]

Second, in cardiac disease, there are chronic compensatory mechanisms, such as dilatation and hypertrophy, that tend to maintain the ejection fraction in the normal range.[34–36] To uncover compensated states and reserve function, it has been suggested that ejection fraction should be determined with stress as well as at rest.[37] Although the prognostic implications of the ejection fraction response to stress are not well established, this approach detects abnormalities that precede a deterioration in the ejection fraction at rest and might serve as an earlier indicator of serious disease.

Finally, the ejection fraction may not directly relate to the presence or absence of heart failure. Heart failure can be considered a clinical expression of elevated atrial pressure and there are important causes of atrial pressure elevation in which systolic function may appear normal, such as volume overload and ventricular inflow obstruction.[4,15,21]

Radionuclide Analysis of Ventricular Function

Ventricular volumes: Radionuclide angiography (either first pass or gated equilibrium) can be used to reliably quantitate the ejection fraction of both the right and the left ventricle.[38–44] Radionuclide techniques may also be used to estimate left ventricular end-diastolic volume. Both area-length (geometric)[43,45,46] and count (nongeometric)[47,48] methods have been reported. Because the radionuclide techniques possess relatively low resolution, these methods only give an approximation of the actual volume. An increase in end-diastolic volume usually reflects ventricular dysfunction and therefore tends to correspond to a decrease in ejection fraction.[49] However, in valvular heart disease, measurement of end-diastolic volume has added importance because it increases early in the course of volume overload, whereas ejection fraction remains normal.[50–52] End-diastolic volume is a measure of preload, which gives perspective to the ejection fraction.[31,32] In addition, stroke volume and end-systolic volume can be calculated from end-diastolic volume and ejection fraction. The stroke volume increases in relation to the degree of volume overload, reflecting an increased ventricular output.[50,51] The end-systolic volume increases when left ventricular contractility is reduced and when afterload is increased and is minimally affected by isolated changes in preload.[21] Some have suggested that the end-systolic volume is actually a better indicator of intrinsic myocardial function than is the ejection fraction.[53,54]

Pulmonary blood volume changes to study ventricular diastolic function: Although the radionuclide angiographic measurement of ejection fraction is a valuable noninvasive index of ventricular systolic function, it does not provide information on diastolic function.[14,15] However, in recent studies, analysis of pulmonary blood volume change from rest to exercise in patients with coronary artery disease was very sensitive in detecting reduced left ventricular function reserve, even more sensitive than ejection fraction.[55,56] The change in pulmonary blood volume is an indirect measure of a change in left atrial pressure during stress. Although as yet untested, this measurement could be valuable in valvular disease, as an indicator of the combined effect of mitral valve function and diastolic ventricular performance.

Clinical Application in Valvular Heart Disease

In this review, the application of radionuclide methods for detection and prognostication in valvular disease will be analyzed. For the purpose of this discussion, the radionuclide findings are most conveniently described under the following general categories: (1) left ventricular pressure overload; (2) left ventricular volume overload; and (3) left ventricular inflow obstruction. In each section, the postoperative findings will also be reviewed. The importance of ventricular function analysis in valvular disease will be discussed, relying on data derived from contrast angiographic and echocardiographic studies as well as radionuclide studies.

Pressure Overload (Aortic Stenosis)

Rest radionuclide angiography: The left ventricular ejection fraction at rest may be normal, increased or decreased in patients with aortic stenosis; however, it remains within the range of normal in the majority of patients (Table I).[34,50] The reason is that the pressure overload usually develops gradually, permitting compensation primarily by concentric hypertrophy.[4,57–59] Occasionally, ejection fraction may be increased with cavity obliteration in systole due most likely to an excessive hypertrophic response.[60–62] This response can

TABLE I

Distribution of Left Ventricular Angiographic Findings in Valvular Heart Disease*

	Ejection Fraction Reduced	End-Diastolic Volume Enlarged	Stroke Volume		
			Reduced	Normal	Increased
Aortic stenosis	37%	14%	15%	85%	0%
Aortic regurgitation	50%†	90%	0%	20%	80%
Mitral stenosis	37%	0%	22%	78%	0%
Mitral regurgitation	22%	65%	0%	38%	62%

* Adapted from Kennedy et al.[50,51] † Approximate values.

be detected by radionuclide angiography.

About 40 percent of patients with aortic stenosis have a reduced ejection fraction and about 15 percent have a left ventricular end-diastolic volume above the normal range.[50] The end-diastolic volume increases in aortic stenosis as a reflection of worsening left ventricular function and this change is parallel with the reduction in ejection fraction. In this situation, prognosis is ominous if the aortic stenosis is not surgically corrected.[63]

Because ejection fraction is known to decrease as a result of increased afterload alone, the reduced ejection fraction in pressure overload may be related to increased afterload as well as to reduced myocardial contractile function.[64–70] The ejection fraction in aortic stenosis is unrelated to the severity of the aortic stenosis (systolic gradient, aortic valve area), but has closely been inversely correlated with mid wall circumferential wall stress, a measure of afterload.[67] Because the compensatory response to increased afterload is hypertrophy to normalize wall stress, myocardial performance at rest is probably primarily determined by the adequacy of adaptation to the increased afterload. Therefore, contractile function in aortic stenosis may not be depressed despite a reduced ejection fraction, but may simply reflect an "afterload mismatch" (increased afterload and inadequate compensatory hypertrophy).[71] This is consistent with pathologic findings in aortic stenosis showing minimal degenerative changes, even when ejection fraction is reduced.[4,72,73] Furthermore, the duration of hemodynamically severe disease during which time degenerative changes might develop tends to be relatively short.[74,75]

Although aortic stenosis affects the left ventricle primarily, it may affect other chambers as well. Patients frequently have poststenotic dilatation of the ascending aorta. The blood pool of the ascending aorta is clearly delineated, although this observation seldom has important clinical implications in patients with aortic stenosis. The right heart is usually not severely affected in aortic stenosis, although in the occasional patient with secondary pulmonary hypertension, right ventricular dilatation might be observed.[76] Further discussion of the effect of secondary pulmonary hypertension on the right heart is included in the discussion on mitral stenosis that follows.

Exercise radionuclide angiography: Borer et al.[77] studied 28 patients with aortic stenosis by supine exercise radionuclide angiography. Although the mean ejection fraction at rest in these patients was normal, the ejection fraction during exercise was below normal and in fact decreased in 25 patients (89 percent). Therefore, although a normal resting left ventricular ejection fraction is usually maintained in aortic stenosis by chronic compensatory mechanisms, the reserve capacity of the left ventricle to respond to additional stress appears to be less than normal.[66,77] Although this response can be used clinically to confirm the presence of severe pressure overload, symptomatic patients with suspected or proved aortic stenosis should not be routinely exercised because of the risk of syncope and sudden death. Furthermore, because the response is similar to that reported in patients with coronary artery disease, exercise radionuclide angiography is not specific for coronary artery disease in the setting of aortic stenosis. Therefore, exercise radionuclide angiography is seldom clinically indicated in patients with aortic stenosis.

Thallium-201 imaging: Thallium-201 studies in aortic stenosis reveal intense tracer uptake by the left ventricular myocardium in relation to the degree of concentric hypertrophy.[78] However, because of low resolution, reliable quantitation of wall thickness and left ventricular mass is only possible with echocardiography.[59]

Because patients with aortic stenosis are frequently older adults and may have symptoms of angina pectoris, exercise thallium-201 studies have been performed to detect the presence of associated coronary artery disease. However, of 11 patients with aortic stenosis without coronary artery disease, 7 (64 percent) had a myocardial defect with exercise,[78] suggesting coronary artery disease. Exercise perfusion abnormalities may develop in patients with aortic stenosis and normal coronary arteries because of an imbalance in myocardial supply and demand known to occur in aortic stenosis[79,80] and because of stress-induced wall thinning, resulting from the decrease in ejection fraction with exercise.[81] For these reasons, exercise thallium-201 imaging is unreliable in detecting or excluding coronary artery disease in association with aortic stenosis.

Thallium-201 imaging at rest, however, may be of value in the patient with aortic stenosis, coronary artery disease and a reduced ejection fraction.[82] In such a patient, the presence of a scar on the thallium-201 scan suggests that a prior myocardial infarction had occurred and that the reduction in ejection fraction was caused, at least in part, by coronary artery disease. However, the absence of a scar suggests that the reduced ejection fraction was primarily a result of the aortic stenosis.

Postoperative studies: In isolated aortic stenosis in the absence of coronary artery disease, surgical risk does not appear to be increased by a reduced ejection fraction preoperatively.[83–85] Furthermore, postoperatively, ejection fraction usually becomes normal, even if the preoperative ejection fraction had been reduced.[83–89] This finding is consistent with prior experimental studies on the effect of removal of afterload on left ventricular function.[68–70] In addition, left ventricular function remains normal on postoperative exercise radionuclide angiographic studies.[77]

Another clinical problem in valvular heart disease is the patient who undergoes aortic valve replacement, improves clinically, yet presents several years later with heart failure. If an artificial prosthesis is present, retrograde contrast left ventriculography may be difficult. In these patients, the degree to which the heart failure is related to a new mechanical overload or myocardial dysfunction can be suggested by radionuclide angiography.[90] With an ejection fraction above 50 percent, a surgically reversible mechanical abnormality is usually the major cause of heart failure. There may be prosthetic valve stenosis or insufficiency or an abnormality of another valve. If the ejection fraction is under

50 percent, myocardial dysfunction is present. A mechanical abnormality may also be present, but there is less likelihood of improvement with surgery.

In summary, radionuclide studies have limited value in the clinical management of patients with isolated aortic stenosis. The reason is that the decision to replace the aortic valve in isolated aortic stenosis is based primarily on patient symptoms, such as angina and congestive heart failure. In addition, surgical results are uniformly excellent, with the ejection fraction returning to normal postoperatively.[5,91] Because of the lack of specificity of exercise radionuclide studies for coronary artery disease, these tests cannot be relied on to detect associated coronary artery disease. Nevertheless, when coronary artery disease is present, radionuclide studies may be of value in evaluating regional wall motion abnormalities and in identifying patients with a worse prognosis after surgery.

Volume Overload (Aortic or Mitral Regurgitation)

Radionuclide angiography at rest: Radionuclide angiographic assessment of left ventricular function is very useful in left ventricular volume overload. In contrast to pressure overload, the severity of the overload itself can be visualized as an increased stroke volume. The following discussion analyzes the pathophysiologic basis for the radionuclide angiographic assessment of ventricular function in volume overload.

Left ventricular volume overload (due to either aortic or mitral valve regurgitation) is characterized by a continuously elevated stroke volume in order to maintain an adequate forward cardiac output.[34] The degree of elevation of the stroke volume is directly related to the regurgitant volume.[50] This has prompted Rigo et al.[92] to suggest that the severity of the left ventricular volume overload can be assessed noninvasively from the left anterior oblique gated equilibrium radionuclide scan, by comparing the regurgitant left ventricular stroke volume with that of the nonregurgitant right ventricle. However, the accuracy of this approach is limited by problems inherent in the radionuclide count analysis of right ventricular stroke volume, such as varying background, scatter, atrial overlap, ventricular size and geometry and edge detection.[43] The increased stroke volume in chronic volume overload is achieved by increased end-diastolic volume (preload), and the Starling effect is used to maintain ejection. As a result, ejection fraction remains normal and is rarely above normal[50–54,93,94] (Fig. 1).

In compensated volume overload, end-diastolic pressure is often normal at an increased end-diastolic volume, indicating that a change in the pressure-volume relation of the ventricle has occurred.[33,93–101] This increase in compliance develops as part of the chronic adjustments to the volume overload. When the volume overload is acute, before adjustments in compliance, the findings are different. End-diastolic pressures are elevated and reductions in ejection fraction are seldom.[4,65,102–104] In patients with these findings, regurgitant volumes are frequently significantly less than those in patients with severe chronic valve regurgitation who have less severe or no congestive symptoms.[103] In contrast, patients with chronic regurgitation have increased compliance and tend to manifest symptoms of heart failure only in association with a reduction in ejection fraction and advanced irreversible left ventricular dysfunction.[16,91]

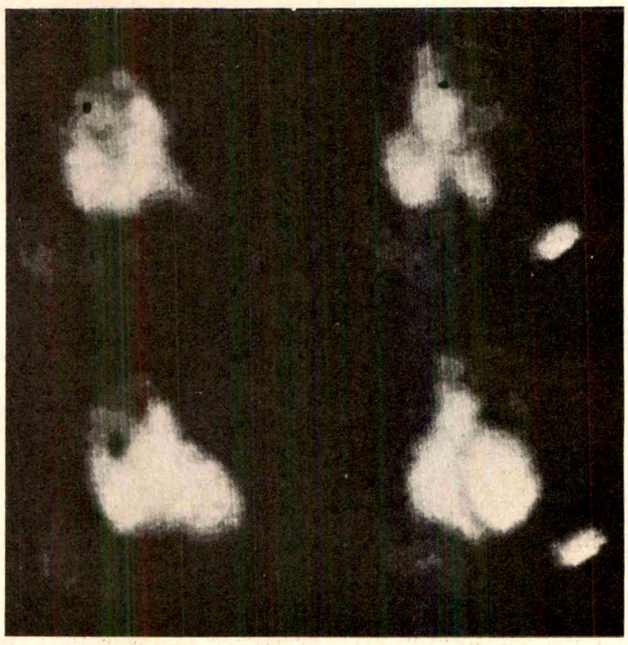


FIGURE 1. Gated equilibrium radionuclide angiogram from a patient with severe aortic regurgitation in the anterior **(left)** and left anterior oblique **(right)** projection. End-systole is **above** and end-diastole **below.** The left ventricular end-diastolic volume and stroke volume are greatly increased. The left ventricular ejection fraction is 61 percent.

In mitral regurgitation, the disparity between acute and chronic forms is somewhat different in that left atrial pressure is increased directly by the regurgitant volume.[94,105–107] Thus, congestive symptoms appear much earlier before left ventricular dysfunction is present than they do in chronic aortic regurgitation. Although adjustments in left ventricular compliance develop with mitral regurgitation, left atrial size and compliance are also major determinants of left atrial pressure.[105–108] Acute mitral regurgitation is characterized by normal sinus rhythm, a normal-sized left atrium and greatly elevated left atrial pressures, whereas chronic mitral regurgitation is characterized by atrial fibrillation, a dilated left atrium and less severe atrial pressure elevation.[51] In extreme left atrial enlargement, left atrial pressure may be normal.[109]

In addition to dilation and increased compliance, another major compensatory response of the left ventricle to chronic volume overload is to increase wall thickness as the chamber dilates. The ratio of wall thickness to chamber radius remains constant, which is termed "eccentric hypertrophy," and is a compensatory mechanism to normalize wall stress.[4,34,57–59,99,110] In addition, the ventricle changes shape from ellipsoidal to spherical, which is another compensatory mechanism to normalize elevated systolic wall stress. The ventricle's shape changes in relation to the reduction in ejection

fraction and indicates that left ventricular dysfunction is present.[57,93,94,99]

Numerous studies have demonstrated that "degenerative" hypertrophic changes develop along with the "physiologic" hypertrophic changes in chronic left ventricular volume overload.[72,73,99,101,110–112] Degenerative changes include fiber slippage and fibrosis, are irreversible and may account for the poor clinical results in some patients after surgical correction of the chronic volume overload.[4,10,83] However, because of the preload augmentation the ejection fraction in chronic left ventricular volume overload may continue to be normal, even in the presence of these irreversible changes.[113]

Afterload is greatly reduced in mitral regurgitation because ejection occurs in part into a low pressure chamber, the left atrium, and nearly half of the regurgitation occurs during "isovolumic" systole before enough pressure is generated to open the aortic valve.[94,107] Afterload in aortic regurgitation is higher than that in mitral regurgitation.[95,114] As a result, end-diastolic volume is larger and ejection fraction is lower in aortic regurgitation compared with mitral regurgitation for a given severity and duration of regurgitation.[4,105] The ejection fraction is reduced in about 50 percent of patients with aortic regurgitation and in only about 20 percent of patients with mitral regurgitation.[50,51] For the same reason, eccentric hypertrophy and degenerative changes are more extensive in aortic than in mitral regurgitation.[4] Degenerative changes are seldom seen in chronic mitral regurgitation unless severe heart failure is present.[112]

Both lesions demonstrate similar changes in left ventricular function in response to pharmacologic alterations in afterload, which may be evident on the radionuclide angiogram.[115–118] Ejection fraction in left ventricular volume overload is inversely related to systolic outflow resistance, which is an important determinant of left ventricular function in these patients.[29]

A difficult clinical problem is the evaluation of a patient with left ventricular volume overload and severe left ventricular dysfunction, as evidenced by a large round, poorly contracting ventricle. The myocardial dysfunction might be secondary to degenerative changes resulting from the regurgitant lesion or, if in excess of that accountable for on the basis of chronic volume overload, there is usually an additional cause, such as associated coronary artery disease.[119] The latter may be suspected on the basis of regional left ventricular wall motion abnormalities, although such abnormalilies, particularly at the left ventricular apex, may develop in chronic left ventricular volume overload with no coronary artery disease as well.[52] A reduced ejection fraction with aortic and mitral regurgitation is associated with a less favorable prognosis, yet there may be symptomatic and hemodynamic improvement after valve replacement in some patients.[121]

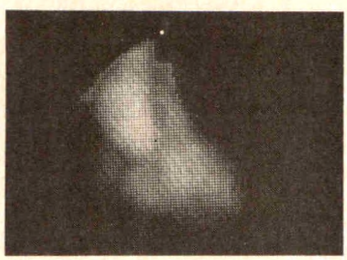


FIGURE 2. End-diastolic image (anterior view) from a patient with mild aortic regurgitation and Marfan's syndrome. The dilated ascending aorta is evident.

Left ventricular volume overload may produce other changes on the blood pool scan in addition to changes in left ventricular volumes. In aortic regurgitation, there is frequently aortic root enlargement with increased pulsations, analogous to that observed during chest fluoroscopy. Furthermore, in aortic regurgitation due to aortic root disease, such as cystic medial necrosis or giant cell aortitis, aneurysmal dilatation of the ascending aorta may be appreciated (Fig. 2). Radionuclide angiography may have an advantage over echocardiography in being able to delineate enlargement of the entire ascending aorta. In mitral regurgitation, the left atrium and right heart are often dilated, as in mitral stenosis (see discussion that follows), in response to chronic elevation in left atrial pressures.

Exercise studies: An important clinical problem is that patients with severe chronic aortic regurgitation may have ventricular dysfunction and yet remain asymptomatic. Such abnormalities are important to discover in asymptomatic patients, because by the time significant symptoms have occurred, potentially irreversible left ventricular dysfunction might have progressed, resulting in a less optimal surgical outcome.[10] Accordingly, noninvasive measurement of ejection fraction with exercise has been proposed as a means of detecting underlying dysfunction in the presence of a normal ejection fraction at rest. Borer et al.[122] have studied the ejection fraction response to exercise in aortic regurgitation. Eight patients with *symptomatic aortic regurgitation* (who are generally considered candidates for valve replacement) all demonstrated a decrease in ejection fraction during maximal supine bicycle exercise. In 22 patients with *asymptomatic aortic regurgitation,* all but one had a normal resting ejection fraction. However, 16 had a subnormal and 6 had a normal ejection fraction response to exercise. The 16 patients with an abnormal ejection response were thought to have exercise-induced left ventricular dysfunction and therefore might be earlier surgical candidates.

The "normal" ventricle increases ejection fraction with exercise because of an ability to increase contractile function, ejecting a larger stroke volume at a similar or lower end-systolic volume (contractile reserve).[15,71] This increase occurs despite increases in heart rate and aortic pressures with exercise, which tend to reduce ejection fraction. A subnormal ejection fraction response usually occurs with an *increase* in end-diastolic volume and suggests underlying ventricular dysfunction. In contrast, the subnormal ejection fraction response to exercise in aortic regurgitation is associated with a *decrease* in end-diastolic volume.[122]

This can be accomplished only by a decrease in stroke volume in excess of the change in end-systolic volume. A reduction in stroke volume in excess of that anticipated due to myocardial dysfunction is consistent with the shortened diastolic filling period and reduced regurgitant volume that occur during increased heart rates and exercise in aortic regurgitation.[22,123] Therefore, a decrease in ejection fraction with exercise is a common finding in severe aortic regurgitation. Patients with early depression of myocardial function who may be surgical candidates are likely to be identified. However, this index may be too sensitive, also identifying patients maximally stressed by large regurgitant volumes, who do not necessarily have underlying myocardial dysfunction.

In a study[124] *in patients with mitral regurgitation,* 10 of 20 patients demonstrated a decrease in ejection fraction with exercise. As with aortic regurgitation, the significance of an abnormal ejection fraction during exercise remains uncertain.

Postoperative studies: Numerous studies have evaluated left ventricular systolic function after correction of aortic and mitral regurgitation.[54,85,125–132] Although clinical response is generally good, the angiographic findings appear to be inconsistent. Nearly all patients demonstrate paradoxical septal motion after valve replacement.[127,133] The mechanism and significance of this finding are unknown.

In addition, after correction of volume overload, the end-systolic volume changes minimally and, as a result, there is a decrease in ejection fraction.[129,132] Several mechanisms have been proposed to explain this apparent reduction in left ventricular function: (1) It may be, in part, a result of the abnormal septal motion that occurs after valve replacement.[127,133] The abnormal septal motion is more likely to affect an M mode echocardiographic assessment of left ventricular function than the nongeometric global approach of radionuclide methods. (2) There may be perioperative damage to the heart.[87,130,134] Although possible, this is not consistent with the lack of decrease in ejection fraction after correction of aortic stenosis or mitral stenosis. (3) The postoperative changes in ejection fraction may reflect altered loading conditions.[87,130] Preload is reduced by eliminating the regurgitant volume. The afterload is probably not changed as dramatically. In aortic regurgitation, there is increased afterload postoperatively due to a residual systolic pressure gradient across the currently available prosthetic valves.[88,113,135] In mitral regurgitation, the increased afterload is a result of removal of the low impedance ejection pathway into the left atrium.[129]

Over the year or two after surgery, there are conflicting data on whether ejection fraction returns to normal or even to preoperative values.[66,83,84,88,125–132] Ejection fraction may remain depressed postoperatively in patients whose ventricles were excessively dilated preoperatively, a finding consistent with clinical studies indicating that severe left ventricular dysfunction and heart failure preoperatively predict a reduced survival postoperatively.[136,137] Because most patients with mitral regurgitation have excellent improvement in functional class postoperatively, the prognostic implications of the reduction in ejection fraction remain uncertain.

The response of the ejection fraction to exercise in the postoperative patient with previously asymptomatic aortic regurgitation has not been reported. Of 10 recently studied patients with *symptomatic* aortic regurgitation and a normal resting ejection fraction preoperatively, 9 had an abnormal ejection fraction with exercise preoperatively and the index remained abnormal in 4 postoperatively. Among 6 *symptomatic* patients with an abnormal resting ejection fraction preoperatively, all had an abnormal ejection fraction with exercise both pre- and postoperatively.[138] The frequent finding of abnormal cardiac reserve in *symptomatic* patients postoperatively is consistent with significant pathologic damage occurring preoperatively as a result of chronic volume overload in these patients.[72]

In summary, radionuclide angiography is valuable in volume overload in both confirming its presence and assessing ventricular function. A depressed ejection fraction at rest implies a poor prognosis and indicates that residual left ventricular function will be present after surgery.[91] End-systolic volume at rest or the ejection fraction response to exercise may be measured serially and may identify patients in whom earlier surgery should be considered. Further studies are needed to define precisely the criteria for optimal timing of valve replacement.

Inflow Obstruction (Mitral Stenosis)

With obstruction to left ventricular inflow, left atrial pressures increase, causing pulmonary congestion, pulmonary hypertension and right ventricular pressure overload.[139,140] The radionuclide angiogram delineates the left atrial and right heart enlargement resulting from this hemodynamic abnormality. Inflow obstruction is typified by mitral stenosis; however, it may also be produced by left atrial myxoma.

Mitral stenosis: Of the four left-sided valve lesions, mitral stenosis has least effect on the left ventricle, causing no major direct hemodynamic stresses on it.[34,141] Nevertheless, 30 to 40 percent of patients with mitral stenosis have a depressed left ventricular ejection fraction.[51,130] This finding is, in part, related to an underfilled ventricle with a decreased preload, leading to a reduced stroke volume. In addition, the reduced left ventricular ejection fraction has also been ascribed to associated rheumatic myocardiopathy and to limitations of left ventricular excursion with a rigid mitral valve apparatus.[1,4,72,142,143] The reduction in ejection fraction does not correlate with the severity of the mitral stenosis.[51]

A frequent consequence of atrial fibrillation is that the sampling of only a few beats on a contrast angiogram or echocardiogram may not accurately indicate left ventricular or right ventricular function.[23] In contrast, the gated equilibrium acquisition, by sampling several minutes of cardiac cycles, provides an average ejection fraction, allowing a better overall determination of left

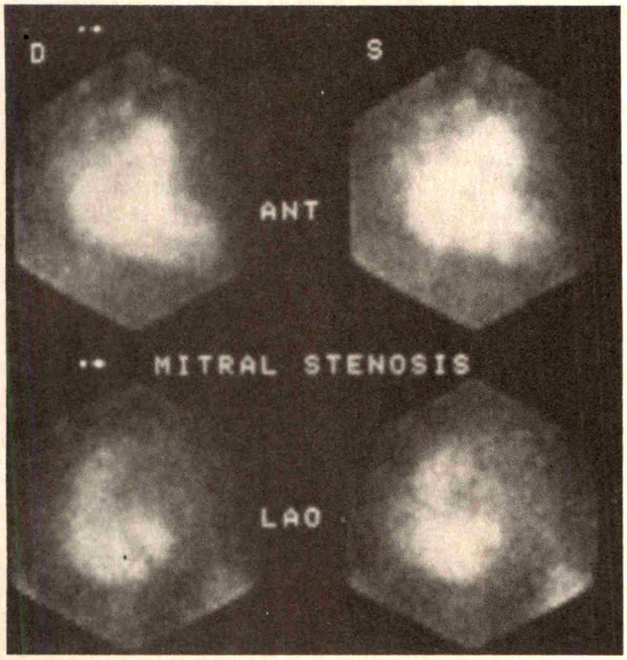


FIGURE 3. Gated equilibrium radionuclide angiogram in a patient with mitral stenosis in the anterior (ANT) and left anterior oblique (LAO) projections. An enlarged right atrium and right ventricle are evident. The left ventricle is reduced in size and the ejection fraction is 59 percent. The left atrium is obscured by overlying chambers in these projections. D = end-diastole; S = end-systole.

ventricular function. Thus, the beat-to-beat variations that occur in atrial fibrillation are eliminated.

Radionuclide angiography as well as echocardiography also demonstrates an enlarged left atrium. The left atrium can best be viewed in a 30° right anterior oblique first pass study and in the left posterior oblique view. It may be totally obscured by overlying chambers in the anterior and 45° to 50° left anterior oblique views of gated equilibrium studies, although it is probably enlarged if it can be seen throughout the cardiac cycle in the left anterior oblique view.

Right ventricular and right atrial enlargement is frequently present. A wide pulmonary arterial segment is evident in patients with increased pulmonary arterial pressure. A representative gated equilibrium scan in a patient with mitral stenosis is shown in Figure 3. In patients undergoing thallium-201 studies, increased thallium uptake in the right ventricle suggests right ventricular hypertrophy.[144,145] However, increased thallium-201 uptake can also occur with acute pressure overload as a result of increased blood flow to the right ventricle.[146]

There is severe pulmonary hypertension in 15 to 20 percent of the patients with mitral stenosis as a result of associated pulmonary arterial vasoconstriction producing a severe pressure overload on the right side of the heart.[115,139,147] When the right ventricle compensates with hypertrophy, its ejection fraction may remain normal.[67] However, if right ventricular systolic pressure rises more rapidly than adequate right ventricular hypertrophy can develop, right ventricular ejection fraction is reduced.[148–151] In addition to the pressure overload, a factor contributing to the reduction in right ventricular ejection fraction is myocardial fibrosis, similar to that found in the left ventricle and a consequence of the rheumatic process.[2,3,72,140]

Tricuspid valve disease may be associated with rheumatic mitral stenosis.[139] This can take the form of tricuspid stenosis, which would be manifested by right atrial enlargement and a right ventricle of normal size and function. Tricuspid regurgitation with concomitant right ventricular volume overload is suggested by right ventricular dilatation and paradoxical septal motion.[152] If the tricuspid regurgitation is primary, the right ventricular ejection fraction is likely to be in the normal range, whereas if it is secondary to right ventricular dysfunction, the right ventricular ejection fraction tends to be dramatically reduced.[153]

Postoperative studies: After correction of mitral stenosis, left ventricular function is generally unchanged.[127,129,130,154–155] As in other patients undergoing cardiopulmonary bypass, paradoxical septal motion is usually evident.[133,152] Although correction of inflow obstruction reduces left atrial pressure and relieves congestive symptoms, an abnormal left atrial pressure may persist after valve surgery, even though it may be less than it was preoperatively.

The following five factors contribute to elevated left atrial pressures postoperatively: (1) preoperative left ventricular dysfunction persisting postoperatively[51]; (2) functional prosthetic mitral valve gradients[135]; (3) postoperative pericardial constriction[156]; (4) residual right ventricular enlargement and dysfunction affecting left ventricular filling[157–159]; and (5) prosthetic valve stenosis or incompetence. With the first factor, left ventricular ejection fraction is reduced, whereas with the last factor a surgically reversible cause for left atrial pressure elevation may be present. As a result, left atrial enlargement and atrial fibrillation usually persist after correction of mitral stenosis.[160]

The presence of severe pulmonary hypertension and right ventricular failure has been correlated with a worse prognosis after mitral valve replacement.[154,155] In patients with these findings, the increased pulmonary vascular resistance is largely dynamic; that is, it is potentially reversible with correction of the left atrial pressure toward normal.[161,162] As a result of removal of the right ventricular pressure overload, right ventricular ejection fraction gradually improves over the year after surgery.[148,149] However, several factors may interfere with the normalization of right ventricular function after surgery: (1) failure of left atrial pressure to return to normal (as discussed previously); (2) persistently elevated pulmonary vascular resistance; (3) irreversible changes in right ventricular function; and (4) uncorrected tricuspid valve disease.

In summary, patients with mitral stenosis often remain in clinically stable condition for many years and the decision to operate is usually based on the presence of class III or IV symptoms.[10,114] Radionuclide angiography is not essential for deciding the timing of surgery in most cases, but is useful in identifying patients with associated right or left ventricular dysfunction, whose

clinical course after valve replacement may be less satisfactory.

Left atrial myxoma. Radionuclide angiography has been shown to detect the presence of and provide an approximation of the size of left atrial myxoma.[163,164] When present, a radiolucent filling defect can be seen in the region of the left atrium. Such tumors are also readily detected by echocardiography. Because left atrial myxoma may produce functional mitral stenosis or regurgitation, or both, the left atrium, pulmonary artery and right ventricle may also appear dilated on radionuclide angiography, as has been reviewed in the discussion of mitral stenosis.[165]

Conclusions

The role of radionuclide tests in clinical practice is still evolving. The presence and severity of valve disease can frequently be determined clinically without noninvasive studies. Similarly, radionuclide approaches may not be necessary in patients in whom valve surgery is clearly indicated. Most frequently, cardiac catheterization provides adequate information. Furthermore, the superiority of radionuclide techniques compared with other less expensive noninvasive approaches remains to be demonstrated.

Nevertheless, radionuclide studies may be very helpful in certain situations. In young patients in whom associated coronary artery disease is unlikely, noninvasive studies combined with other clinical data may replace preoperative cardiac catheterization in valve disease and left atrial myxoma. In patients with heart failure, precatheterization radionuclide angiography can delineate chamber size and function, which may expedite catheterization and may substitute for invasive contrast angiographic assessment of ventricular function. Furthermore, the demonstration of a reduced ejection fraction is of prognostic significance. Radionuclide studies are particularly helpful in determining the relative contribution of mechanical factors and myocardial dysfunction to cardiac insufficiency.

Accordingly, our current approach to the patient with valve disease is first to evaluate carefully routine clinical data. If additional noninvasive information might be useful, echocardiography would be performed next because of its lower cost, lack of radiation exposure and superior resolution compared with nuclear techniques. Radionuclide angiography is then performed if the echocardiogram does not provide adequate information about global and regional ventricular function; if a study during exercise might be useful, thallium-201 imaging is used to identify myocardial scars in patients with abnormal ventricular function. Only continued clinical investigation will allow determination of the precise role of these studies in the clinical evaluation of patients with valvular heart disease.

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Two Dimensional Echocardiography in Mitral, Aortic and Tricuspid Valve Prolapse

The Clinical Problem, Cardiac Nuclear Imaging Considerations and a Proposed Standard for Diagnosis

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The mitral valve prolapse syndrome may present with a variety of clinical manifestations and has proved to be a common cause of nonspecific cardiac symptoms in clinical practice. Primary and secondary forms must be distinguished. Myxomatous degeneration appears to be the common denominator of the primary form. The diagnostic standard of this form has not previously been defined because the detection of mitral leaflet tissue in the left atrium (prolapse) on physical examination or angiography is nonspecific. M mode echocardiography has greatly enhanced the recognition of this syndrome but has not proved to be the best diagnostic standard because of its limited view of mitral valve motion. The advent of two dimensional echocardiography has provided the potential means for specific identification of the mitral leaflet motion in systole and can be considered the diagnostic standard for this syndrome. Primary myxomatous degeneration with leaflet prolapse is not localized to the mitral valve. Two dimensional echocardiography has detected in preliminary studies tricuspid valve prolapse in up to 50 percent and aortic valve prolapse in about 20 percent of patients with idiopathic mitral valve prolapse.

In the 1930's controversy raged as to whether the mid systolic nonejection click originated from an extracardiac source or from the mitral valve.[1–3] It was not until the beginning of 1960 that Reid[4] proposed that the systolic click was due to a "chordal snap" and that the mid to late apical systolic murmur represented mitral regurgitation.[5] Barlow and his coworkers[6,7] were the first to associate the mid systolic click, late systolic murmur and accompanying abnormal electrocardiographic features with specific angiographic findings and suggested the syndrome of mitral valve prolapse. Clinical features of this new syndrome were well described in the mid 1960s by Hancock and Cohn.[8]

The Clinical Problem

The extensive clinical experience of Jeresaty[9] and Barlow and Pocock[10] support a classification of mitral valve prolapse into primary and secondary forms. Secondary mitral valve prolapse results from an abnormality of the six elements that form the basis of normal mitral valve integrity.[11] This may be caused by myocarditis, rheumatic endocarditis or primary cardiomyopathy. Primary or idiopathic mitral valve prolapse includes a spectrum that ranges from mild prolapse of one or more mitral leaflets without associated symptoms to severe prolapse of one or more cardiac valves, usually with severe valve regurgitation. The latter condition has been termed "floppy valve syndrome."[12,13] Patients whose condition is in between these two ends of the spectrum frequently have cardiovascular symptoms and may be considered as having symptomatic,

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idiopathic or primary mitral valve prolapse or (as recommended by Barlow and Pock[10]) the billowing mitral leaflet syndrome.

The anatomic features of primary mitral valve prolapse include large redundant, scalloped and thickened valve cusps associated with histologically defined myxomatous degeneration of the valve tissue and associated anular dilatation.[9] The myxomatous degeneration, which produces a loss of the collagenous support, allows for leaflet stretching and subsequent prolapse during systole of the atrioventricular valves and during diastole of the semilunar valves. Whether myxomatous degeneration is due to unidentified local factors or to a primary defect in mucopolysaccharide metabolism is unknown. The presence of myxomatous degeneration is the common denominator of the spectrum of primary mitral valve prolapse that differentiates primary from secondary prolapse states.[9] Secondary mitral valve prolapse is chiefly an angiographic finding.[9]

The possibility that primary mitral valve prolapse may be due to a primary myocardial abnormality has been suggested because of the presence in some patients of left ventricular asynergy,[14] abnormal left ventricular hemodynamics[15] and myocardial lactate abnormalities.[16] Underdevelopment of the left circumflex coronary artery[17] and a "corkscrew" coronary appearance[18] have not been confirmed.[19] Left ventricular asynergy may be due to an artifact of angiography, ventricular arrhythmia or traction on the papillary muscle because 72 percent of patients with the primary mitral valve prolapse syndrome have normal left ventricular contractility.[20] Abnormal myocardial metabolism may be due to papillary muscle ischemia.

The Clinical Syndrome

Prevalence

Primary mitral valve prolapse has been observed virtually at any age[9] although it appears to be most common in the 3rd to 5th decades of life. Approximately two thirds of the patients are female in the younger age group, whereas the sex prevalence becomes equal in the middle to older age group.[21] On the basis of echocardiographic criteria[22] approximately 50 percent of first degree relations have mitral valve prolapse, suggesting that the genetic pattern may be one of autosomal dominant inheritance. The usual lack of familial occurrence may be the result of underestimation due to silent or asymptomatic forms. The prevalence of primary mitral valve prolapse depends on the standard used for its diagnosis. On the basis of auscultation (systolic click or mid to late systolic murmur, or both) the prevalence rate ranges from 0.4[23] to 17 percent.[9,24] Approximately 5 percent of autopsies performed routinely on patients over 40 years of age have shown redundant mitral leaflets.[25,26] The use of M mode echocardiographic criteria has defined a prevalence range of mitral valve prolapse of 4.4[27] to 21 percent.[24] The reported studies differed in the nature of the recruitment of their study populations. Probably the best defined prevalence rate in young women was reported by Procacci et al.,[28] who found mitral valve prolapse in 6.3 percent of 1,169 wives of Air Force personnel. Jeresaty[9] points out that in view of the known female preponderance in these studies a 4 percent prevalence rate in the general population can be extrapolated.

Clinical Features

Symptoms: The prevalence of symptomatic versus asymptomatic primary mitral valve prolapse has not been defined because a diagnostic standard has not been established. One of the most troubling symptoms in mitral valve prolapse is chest pain, which occurs in approximately 50 percent of patients[29] and is usually atypical for angina pectoris, although occasionally it may be quite classic.[18] In Jeresaty's series,[30] 61 percent of patients had chest pain; the pain was unrelated to exercise in 83 percent, exertional in 8 percent and evident on both rest and exertion in 9 percent. Chest pain may be due to papillary muscle ischemia resulting from marked traction on the papillary muscles by the prolapsing leaflets and their chordae tendineae, in light of the tenuous blood supply to the papillary muscle itself.[9] The possibility of coronary spasm has been suggested by Cobbs.[31]

Fatigue and dyspnea have been reported in 9[29] to 60 percent[30] of patients. The etiology is unknown but the possibility of psychoneurotic hyperventilation[32] has been considered. Palpitations, dizziness or presyncope occurs in one third to one half of patients.[30] Such symptoms are often due to arrhythmia[33] but frequently are reported during documented normal sinus rhythm.[33] Frank syncope has been associated with ventricular fibrillation,[33,34] and this symptom usually demands evaluation with Holter monitoring. The psychiatric symptoms of anxiety and lassitude have been noted in 15[30] to 38 percent[32] of patients. It appears, as suggested by Wooley,[35] that many patients previously described as having DaCosta's syndrome, neurocirculatory asthenia or soldier's heart syndrome may, in fact, have idiopathic mitral valve prolapse. Transient ischemic attacks have been reported[36] and may be due to cardiac emboli in light of Pomerance's finding[37] of fibrin and blood cells adherent to the myxomatous valve.

Physical examination: In patients with primary mitral valve prolapse the cardiac examination may be entirely normal, which was the case in 17 percent of Jeresaty's series.[9] The systolic nonejection click may occur early (1 percent), be isolated to mid to late systole (53 percent) or be associated with a mid to late systolic murmur (17 percent). Of Jeresaty's 315 patients,[9] 2 percent had a late systolic murmur as an isolated event and 1 percent had a precordial whoop or honk. A pansystolic murmur was present in 9 percent, although in older patients this finding was present in up to 25 percent of cases.[38] The systolic click in mitral valve prolapse has been shown to coincide with the maximal prolapse of the mitral valve[39] and is probably due to sudden tightening of the chordae tendineae, which has been termed a chordal snap.[4] Tensing of the inverted leaflet producing a snapping sail phenomenon[40] and sudden deceleration of blood mass and vibrations of the cardiac structure[41] are potential additional causes. The mid to

late systolic murmur is usually due to mitral regurgitation.[9] Provocative maneuvers that alter the critical left ventricular volume at which prolapse occurs will displace the location of the systolic click and duration of the systolic murmur.

Additional physical findings include abnormalities of the bony skeleton with kyphosis, pectus excavatum or scoliosis. The body habitus is usually asthenic and a particular dermatoglyphic pattern may occur in which there is an increased prevalence and distribution of "arches."[42]

Electrocardiographic findings: Abnormalities seen in the routine 12 lead scalar electrocardiogram include nonspecific repolarization abnormalities in approximately 33 percent of patients,[18,30,43] although in large surveys these have been seen in approximately 15 percent.[24,28] The prevalence rate of a prolonged Q-T interval has ranged from 7.5 to 47 percent.[9] Abnormalities of rhythm detected with Holter ambulatory monitoring include up to a 75 percent prevalence rate of ventricular arrhythmias and a 50 percent prevalence rate of atrial arrhythmias.[33,44,45] The sick sinus syndrome and conduction abnormalities have been noted[9] as well as atrial fibrillation, supraventricular tachyarrhythmias and the Wolff-Parkinson-White syndrome.[18,21,46,47] Arrhythmias may be due to tensing of the mitral leaflet tissue itself with resultant stimulation of electrically active fibers within the leaflets.[48] Chordae tendineae-induced mechanical stimulation of the endocardium[49] and associated endocardial lesions[50] are additional possibilities.

Cardiac Nuclear Imaging Considerations

Exercise-induced S-T segment abnormalities have been seen in 10 to 60 percent of patients with mitral valve prolapse and a history of chest pain.[21] Radionuclide studies developed for detection of myocardial ischemia have also been used to evaluate patients with mitral valve prolapse. These studies have attempted to assess whether a sufficient mass of myocardium becomes ischemic during exercise stress to cause detectable abnormalities in patients with mitral valve prolapse. Such observations would be important in understanding the physiologic mechanism of exercise-induced chest pain and electrocardiographic abnormalities in these patients. In addition, the influence of the presence of mitral valve prolapse on the accuracy of these studies in the diagnosis of coronary artery disease is important because of the frequent coexistence of these two disorders.

Thallium-201 imaging: Myocardial imaging with thallium-201 during rest and exercise has been reported in three studies[51–53] involving 69 patients. Concomitant coronary artery disease was documented in 17 of these 69 patients and 16 of the 17 patients had an exercise-induced perfusion defect on thallium-201 imaging. In contrast, all 52 patients with normal coronary arteries and mitral valve prolapse had a normal distribution of myocardial blood flow.

Nuclear angiography: Newman et al.[54] assessed left ventricular function during rest and exercise in patients with mitral valve prolapse. Six of 11 such patients with angiographically demonstrated coronary arterial stenosis exhibited wall motion abnormalities and decreased left ventricular ejection fraction during exercise. This abnormal response to exercise was similar to that observed in patients with coronary artery disease alone. In contrast, 11 patients with mitral valve prolapse demonstrated on echocardiography and 12 with mitral valve prolapse and normal coronary anatomy demonstrated angiographically exhibited increased left ventricular ejection fraction and normal wall motion during exercise. These radionuclide studies suggest that in patients with mitral valve prolapse and normal coronary arteries sufficient ischemic myocardium does not develop during exercise to be demonstrated by thallium-201 imaging or by measurements of left ventricular function. Moreover, the presence of concomitant mitral valve prolapse in patients with coronary disease does not appear to diminish the diagnostic accuracy of these methods of detecting myocardial ischemia.

Treatment

The treatment of mitral valve prolapse is directed toward relief of chest pain and arrhythmias, particularly when the latter are associated with cardiovascular symptoms. Propranolol is the drug most commonly used initially because it decreases left ventricular contraction thereby causing increased left ventricular volume and a subsequent decrease in the severity of prolapse.[55] Patients frequently do not tolerate large doses of propranolol and the usual range of effective dosage is 40 to 80 mg/day.[9] The use of nitrates (for chest pain) or specific antiarrhythmic agents may need to be considered.[9] Mitral valve replacement for severe mitral regurgitation with associated left ventricular dysfunction may be necessary and is associated with an increased prevalence of valvular dehiscence because of myxomatous degeneration in the mitral valve anulus.[9]

The general prognosis for patients with mitral valve prolapse appears to be benign, although patients with a late systolic murmur are more likely to have complications.[56] The latter include sudden death, infective endocarditis, progressive mitral regurgitation, acute chordal rupture with resultant acute severe mitral regurgitation, and transient ischemic attacks.

Diagnosis of Mitral Valve Prolapse

Angiocardiography as the standard? To date, there has been no uniform agreement on what constitutes a diagnostic standard for the identification of primary mitral valve prolapse. Because the condition is relatively benign, surgical or necropsy data are rarely available in patients presenting with cardiac symptoms in whom mitral valve prolapse is suspected. Before the advent of echocardiography, the diagnosis had to be established by physical examination or by electrocardiographic or angiocardiographic features. Some have recommended that left ventricular cineangiography be considered the diagnostic standard with which other diagnostic methods are compared.[57] However, the normal mitral valve has variable motion patterns on left

ventricular angiography and the usual right anterior oblique left ventriculogram is unable to define anterior mitral leaflet prolapse in most cases.[9] Smith et al.[58] demonstrated the presence of angiographic mitral valve prolapse in 40 percent of patients with ischemic heart disease, 32 percent of patients with rheumatic heart disease, 10 percent of patients with cardiomyopathy, 42 percent of patients with congenital heart disease and 60 percent of patients with chest pain and normal coronary arteries. Interobserver variability in the detection of mitral valve prolapse by preset angiographic criteria is extremely high.[59] Most investigators believe that angiography is not a perfect tool[60] and that the diagnostic definition by angiography of mitral valve prolapse is ill defined and nonquantifiable.[61] Thus, angiography does not appear to be an acceptable diagnostic standard for the identification of primary mitral valve prolapse.

Systolic click as the standard? Jeresaty[9] has argued that the systolic nonejection click should be used as the reference for the diagnosis of mitral valve prolapse. However, he noted that the presence of mitral valve prolapse as defined by angiographic and other criteria may be silent on auscultation in up to 17 percent of cases.[9] In addition, the abnormal physical findings are not pathognomonic because the nonejection systolic click may occur in pneumothorax,[62] atrial myxoma,[63] aneurysm of the interventricular septum[64,65] and idiopathic hypertrophic subaortic stenosis[66]; and the mid to late systolic murmur due to mitral regurgitation has many causes.

Is echocardiography the diagnostic standard? Because primary mitral valve prolapse is caused by myxomatous degeneration and loss of collagenous support of mitral valve leaflets that allow them to prolapse into the left atrium, the actual identification of mitral tissue that is in the left atrium during systole should be considered the hallmark of this disorder. Obviously, findings on the physical examination are nonspecific and the inherent variability and difficulty of angiography of the left ventricle limits this technique as a means of identifying the "prolapsed tissue." The ability of diagnostic echocardiography to image the mitral valve and to define location of mitral leaflet tissue during diastole and systole (in terms of whether prolapse into the left atrium has occurred) suggests that this method has the potential for providing a diagnostic standard.

New techniques are often compared with currently available techniques to determine their accuracy in diagnosis. However, when new techniques are better able to identify a particular diagnostic problem, their comparison with established techniques with inherent faults and limitations may not necessarily be of diagnostic value.

Echocardiography in Mitral Valve Prolapse

M Mode Echocardiography

Posterior systolic buckling and hammocking displacement of mitral leaflet: Shah and Gramiak[67] were the first to describe in detail posterior mid systolic buckling of the mitral valve and a posterior hammocking displacement of the mitral leaflet during systole as the M mode echocardiographic hallmarks of the prolapsed mitral valve (Fig. 1). Dillon et al.[68] and Kerber et al.[69] similarly described the M mode echocardiographic feature of posterior buckling in mid systole, which they also considered specific for mitral valve prolapse. However, the technical aspects of M mode echocardiography are extremely important to consider in regard to the potential false positive and false negative induction of these echocardiographic findings. Markiewicz et al.[24] demonstrated that a transducer placed high on the chest wall and angled caudad may produce a D point posterior to the C point with the mitral valve ring and leaflets moving perpendicular to the echocardiographic beam away from the transducer producing a false positive posterior dipping of the mitral valve. Conversely, if the transducer is low on the chest wall and pointed cephlad, the posterior mitral leaflet may not be visualized and the anterior mitral valve motion may mask mitral valve prolapse with the D point anterior to the C point, thus producing a false negative study. However, with proper M mode echocardiographic technique, the presence of midsystolic buckling even with no evidence of mitral valve prolapse on angiography or physical examination is accepted by most workers in the field as diagnostic of mitral valve prolapse.[9] Pansystolic hammocking (Fig. 2) has been considered less specific,[70] with some investigators[24] using 2 mm of posterior displacement as a diagnostic criterium of mitral valve prolapse, whereas others[27] have suggested up to 5 mm as a criterion. Such rigid criteria may increase the specificity, but a decrease in sensitivity will result. Jeresaty[9] has therefore recommended a criterion of a minimum of 3 mm of leaflet sagging to obtain the best concomitant specificity and sensitivity.

The determination of sensitivity in the diagnosis of mitral valve prolapse with M mode echocardiography as compared with other standards has been attempted. When positive auscultatory findings are used as the diagnostic standard of mitral valve prolapse, M mode echocardiography will be positive for prolapse in only 19 percent of patients.[59] However, the sensitivity of the M mode study ranges from 54 to 82 percent[24,29,71] when left ventricular angiographic findings are used as the standard. A false negative M mode echocardiograhpic study may result from poor quality echocardiograms, a transducer too low on the chest wall or lack of full visualization of the mitral valve leaflets due to the limited "ice pick" view; furthermore, the prolapsing mitral leaflets move not only posteriorly but also superiorly and if prolapse is primarily in the superior plane, M mode echocardiography cannot recognize its presence. False positive M mode echocardiographic evidence of mitral valve prolapse producing a pansystolic hammocking motion can occur in pericardial effusion[72,73] (due to swinging of the heart) or mitral stenosis[74] or may be a result of location of the transducer high on the chest wall.[24] Although prolapse of the posterior leaflet was originally[69] considered most common on the basis of M

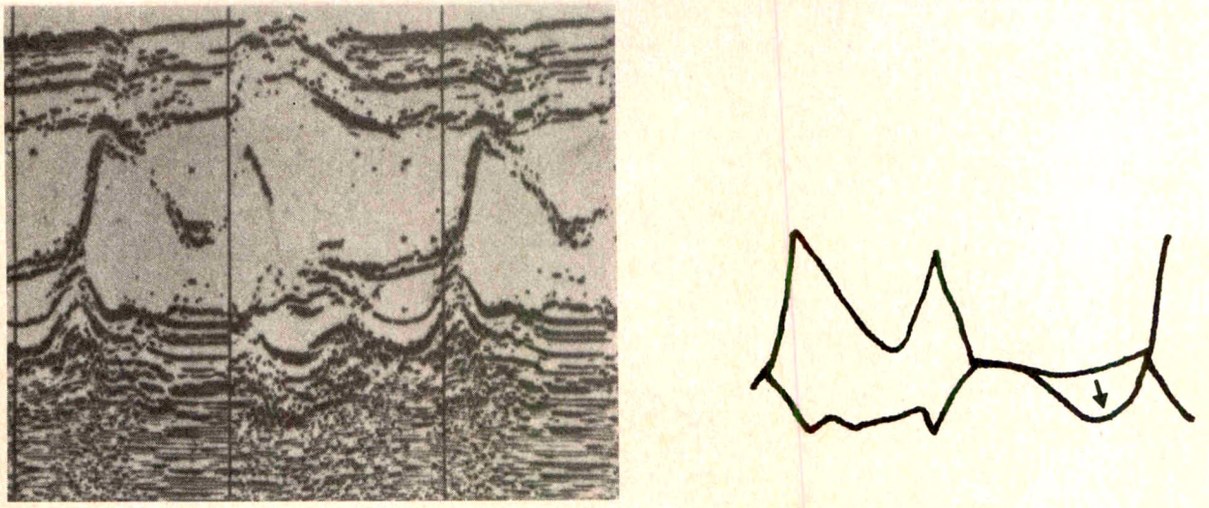


FIGURE 1. Mitral valve prolapse. M mode echocardiographic representation of the mitral valve demonstrating, during systole, mid systolic posterior buckling (**arrow in diagram**) of the posterior mitral valve leaflet as seen in mitral valve prolapse.

mode echocardiographic criteria, it is now clear that both leaflets are prolapsed in the majority of cases.[75–77] No correlation among the degree of mitral regurgitation, the location of prolapse on M mode echocardiography and the presence of a click or murmur, or both, on physical examination has been found.[78]

Other M mode echocardiographic features of mitral valve prolapse: These have included an increased amplitude of the mitral valve excursion of more than 22 mm (with an anterior mitral valve leaflet butting against the interventricular septum in early diastole).[57,59,70] In addition, more than three systolic echoes, usually due to redundant or multiscalloped leaflets and occasional thickening of the mitral valve leaflet, have been suggested.[59,77] Multiple diastolic echoes similar to those seen in atrial myxoma were recently described and were thought to be due to the posterior leaflet's curling under the anterior leaflet in diastole.[79] In addition, mitral leaflet collapse posteriorly toward the left atrium[76] and the observation of fragments of the mitral leaflets in the left atrium[59] also suggested mitral valve prolapse. Shaggy echoes due to redundant leaflets with multile echo-reflective surfaces may exist on the mitral valve during diastole with or without the presence of vegatations due to infective endocarditis.[80,81] Systolic anterior mitral valve motion may be seen in mitral valve prolapse caused either by chordae tendineae[82] or by superimposition of echoes.[83]

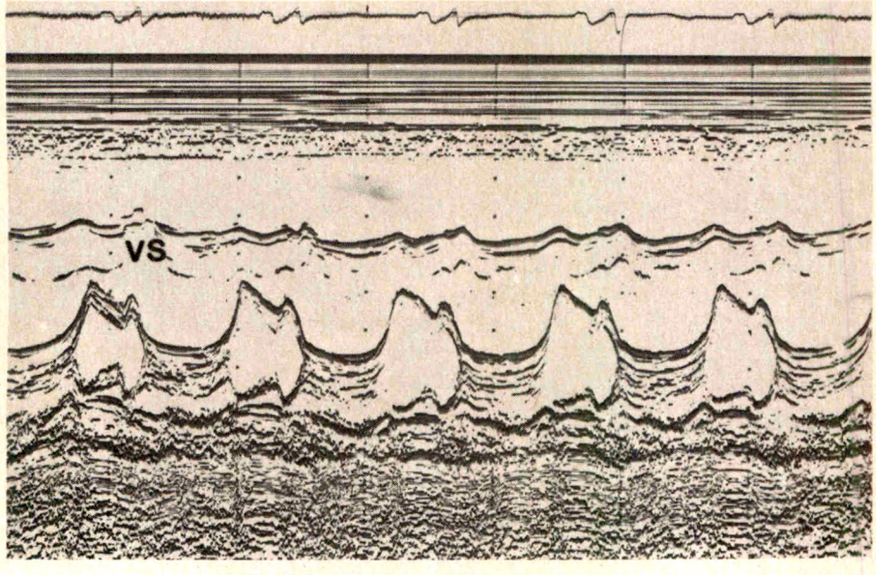


FIGURE 2. Mitral valve prolapse. M mode echocardiographic representation of the mitral valve demonstrating, during systole, holosystolic posterior motion (hammocking) with multiple systolic echoes suggestive of mitral valve prolapse. VS = ventricular septum.

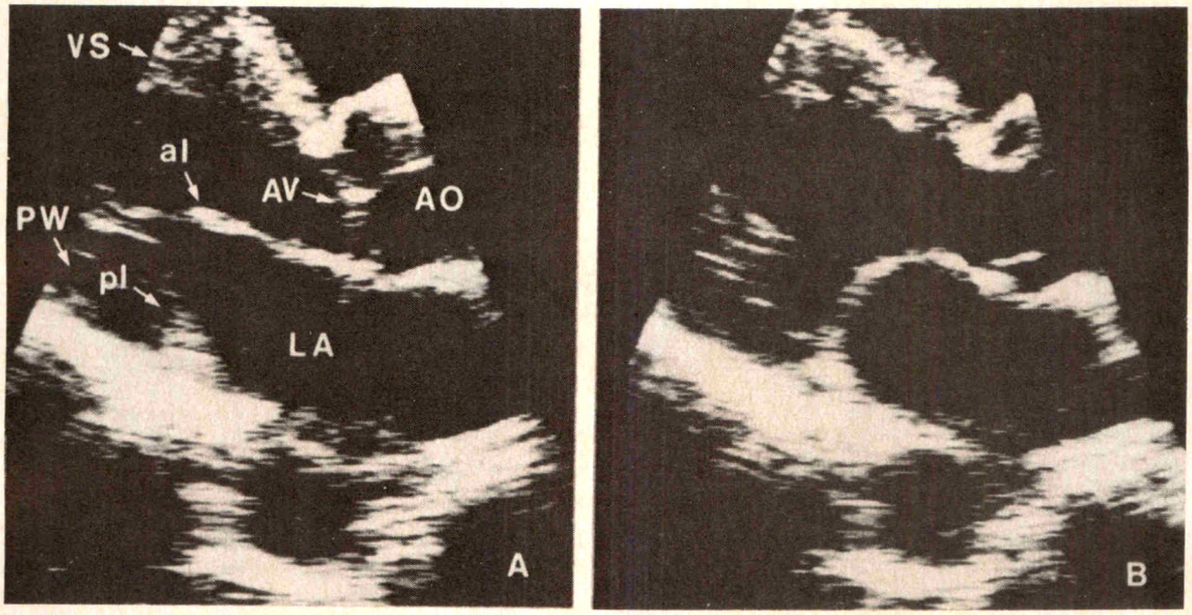


FIGURE 3. Normal mitral valve. **A,** longitudinal left ventricular long axis stop frame view in diastole. The aortic valve (AV) is in the closed position and the mitral valve anterior leaflet (al) and the posterior leaflet (pl) are in the open position. AO = aorta; LA = left atrium; PW = posterior wall; VS = ventricular septum. **B,** the mitral valve in systole. The anterior and posterior leaflets lie in the left ventricular cavity inferior to the mitral valve ring. The aortic valve is in the open position.

Two Dimensional Echocardiographic Studies

Although M mode echocardiography has theoretic advantages over angiography or physical examination as the diagnostic means of identifying mitral valve prolapse, the limitations cited make this tool imperfect. Thus, until recently no single technique has provided the cardiologist with the best single diagnostic standard. The advent of two dimensional echocardiography may have changed this fact.

Combined superior and posterior prolapse of the posterior leaflet: Sahn et al.[83] using two dimensional echocardiographic studies clarified many of the problems of M mode echocardiography by finding that the prolapsing motion of the mitral valve occurs in a superior as well as a posterior direction; the body of the posterior leaflet may be driven superiorly toward the left atrium while portions of the mitral leaflet near the atrioventricular junction move posteriorly. M mode echocardiographic mid systolic discrete prolapse and holosystolic hammocking were both clearly demonstrated in the same patient and could be produced by differences in beam angulation. Multiple echo lines as seen on M mode echocardiography are due to the ultrasonic beam's intersecting the arched or prolapsed mitral leaflet more than once as the beam subtends different portions of the leaflet at the same time. Systolic anterior motion on M mode echocardiography appeared to result from superimposition of echoes from the mitral anulus as well as from the posteriorly superior arched prolapsed leaflets. False negative M mode echocardiographic criteria for mitral valve prolapse could easily be differentiated by two dimensional echocardiographic demonstration of true superior prolapsed motion of the body of the mitral leaflets. Practically, two dimensional echocardiography can be considered the diagnostic standard for mitral valve prolapse in light of its ability (1) to demonstrate the superior and posterior arching of mitral valve leaflets that are present in patients with mitral valve prolapse syndrome and (2) to differentiate this motion from other causes of horizontal positioning of the leaflet tissue that create false positive patterns on M mode echocardiography.

Anterior versus posterior leaflet prolapse: Gilbert et al.[84] utilized phased array real time two dimensional echocardiography to identify spatial orientation of cardiac structures to provide clear details of the motion characteristics of the mitral valve in patients with angiographically proved mitral valve prolapse. Their study evaluated only the left ventricular longitudinal tomographic cross-sectional view. In normal control subjects without prolapse on cardiac catheterization, analysis of mitral valve motion during systole revealed that no superior movement ("prolapse") of the leaflets occurred above the level of the atrioventricular ring (Fig. 3). Gilbert et al.[84] also demonstrated that the most reliable indicator of mitral valve prolapse was the finding on two dimensional echocardiography of superior motion of either one or both mitral valve leaflets above the level of the mitral ring in systole (Fig. 4 and 5). Displaced posterior coaptation was an additional observation. On angiography 23 patients had anterior and posterior leaflet prolapse. However, on two dimensional echocardiography 29 patients had both anterior and posterior leaflet prolapse, whereas 4 had isolated posterior and 1 isolated anterior mitral leaflet prolapse. Thus, nine patients had two dimensional echocardiographic evidence for anterior leaflet prolapse that was missed on angiography. Seven of the 29 patients had entirely normal M mode echocardiograms, suggesting that two dimensional echocardiography is far more sensitive than M mode echocardiography in detecting mitral valve prolapse. The lack of sensitivity by angiography has been previously cited and, since the anterior leaflet is difficult to define on angiography because it is superimposed on the opacified silhouette of the left ventricle, it is not surprising that two dimensional echocardiograhy is

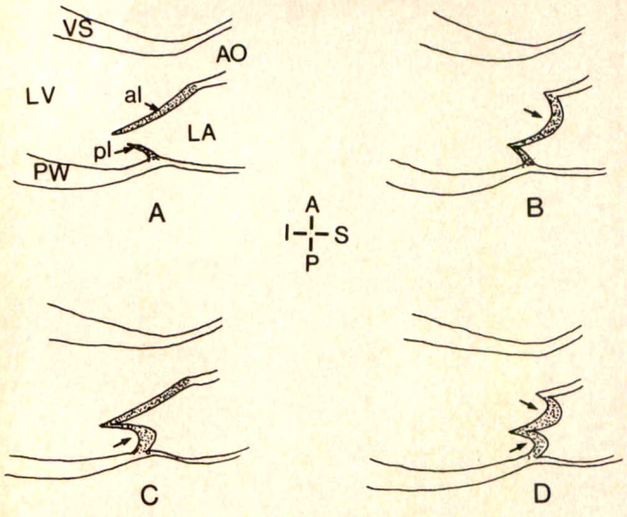


FIGURE 4. Mitral valve prolapse. **A,** schematic drawing of the left ventricular long axis view in a patient without prolapse. The mitral valve anterior leaflet (al) and posterior leaflet (pl) lie within the left ventricular cavity in systole. **B,** anterior mitral valve leaflet prolapse (**arrow**). The anterior leaflet is within the left atrium superior to the mitral valve ring in systole. **C,** isolated posterior mitral leaflet prolapse (**arrow**). The posterior leaflet is in the left atrium during systole. **D,** prolapse of both the anterior and posterior leaflets. During systole, both leaflets are situated in the left atrium superior to the mitral valve ring. A = anterior; I = inferior; LV = left ventricle; S = superior; P = posterior; other abbreviations in Figure 3.

able to identify more clearly the presence of mitral valve prolapse.

Potential limitations of the method: Theoretically, the standard left ventricular longitudinal cross-sectional view has potential limitations in that the mitral ring is obliquely imaged and the lack of fixed adjacent landmarks renders the analysis of mitral motion in reference to the mitral ring difficult. Excessive atrivoventricular groove motion that can be seen in mitral valve prolapse also adds to the difficulty in analyzing posterior leaflet motion with this view. Technical difficulties in properly angling the transducer on the mitral valve with medial and tangential cuts across the mitral valve orifice may cause false positive findings of abnormally posterior coaptation and superior arching of the mitral valve leaflets. The recent definition of the apical four chamber view[85] has provided an additional approach to the analysis of mitral valve motion. The mitral ring in a properly obtained apical view is horizontal and perpendicular to the interventricular septum and, therefore, the motion of the leaflets and location of the coaptation point can be clearly analyzed in relation to the plane of the mitral valve ring. The hyperkinetic atrioventricular groove motion is usually absent from the apical view and thus does not interfere with analysis of the motion of the posterior leaflet.

Analysis of 105 subjects with echocardiographic diagnosis of mitral valve prolapse: We therefore investigated the role of two dimensional echocardiography using the apical four chamber view in the diagnosis of mitral valve prolapse in light of these advantages.[86] A control group was analyzed consisting of 19 patients with normal findings on left ventricular cineangiography and 5 patients with idiopathic congestive cardiomyopathy. Neither the apical nor the left ventricular longitudinal view in these patients revealed that the mitral valve's anterior or posterior leaflets lie above the atrioventricular ring (toward the left atrium) during systole (Fig. 4 and Fig. 6, top). One hundred five subjects without evidence of structural heart disease were identified (by retrospective review of 900 two dimensional echocardiographic studies) who had mitral valve leaflet motion patterns that showed prolapse into the left atrium in systole in either the left ventricular longitudinal or apical views. The mean (± standard deviation) age of these 105 patients was 40 ± 17 years and 67 percent were female. Ninety-five had prolapse of both anterior and posterior mitral valve leaflets; the apical view revealed prolapse of the anterior mitral leaflet in 93 of 99 subjects while the left ventricular longitudinal view demonstrated prolapse of the anterior leaflet in only 45 of 99 ($p < 0.01$). Of the 101 patients with prolapse of the posterior mitral valve leaflet 84 were detected with the apical and 73 by the left ventricular longitudinal view (p = NS). These data suggest that the apical tomographic two dimensional echocardiographic view appears to be superior to the left ventricular longitudinal view for the detection of anterior leaflet prolapse.

Grading of severity of prolapse: When one utilizes an arbitrary grading system of mild, moderate and severe prolapse, additional information is derived. Mild mitral valve prolapse was defined when the coaptation point of both leaf-

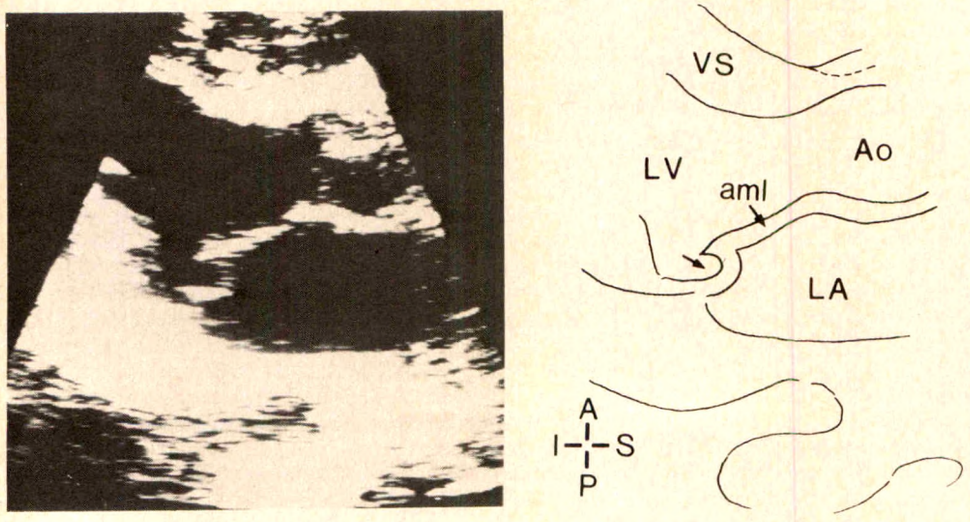


FIGURE 5. Left ventricular long axis view of the mitral valve. The anterior mitral valve leaflet (aml) is not prolapsed, whereas the posterior leaflet (**isolated black arrow**) is situated in the left atrium in systole. Abbreviations as in Figure 4.

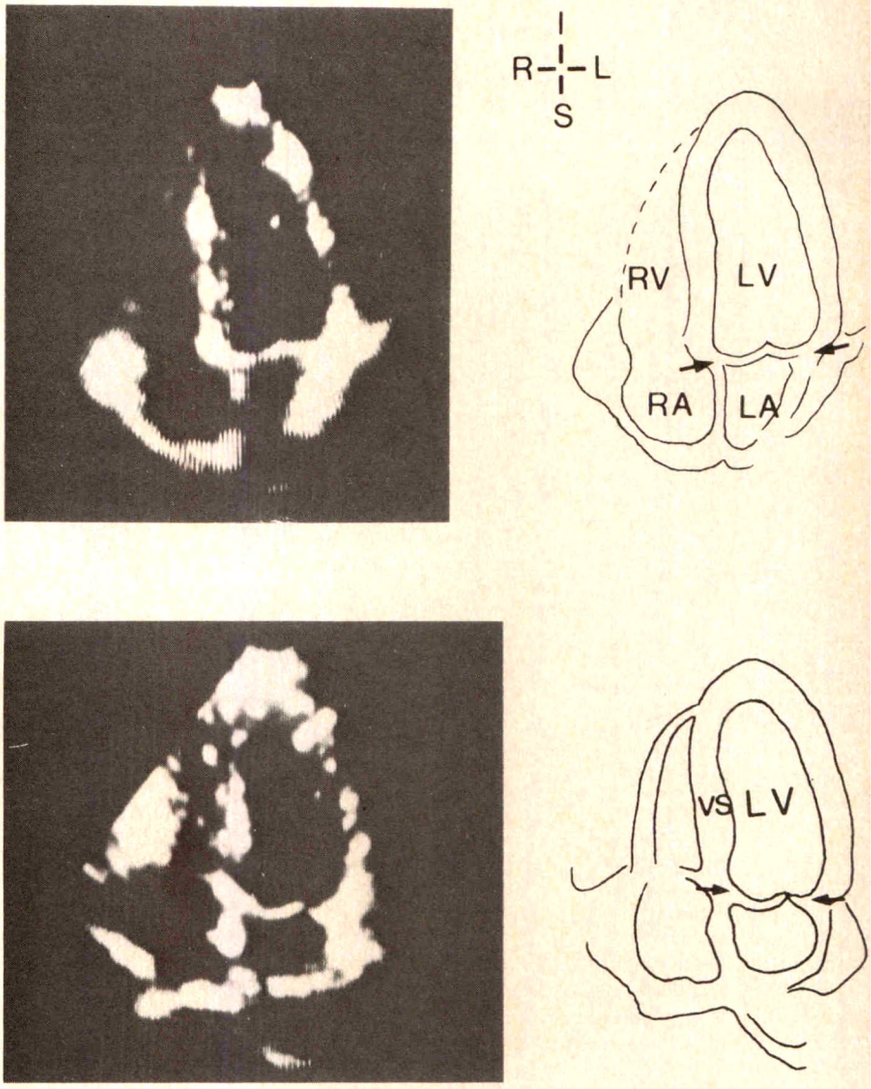


FIGURE 6. Four chamber apical views. **Top,** from a subject without mitral valve prolapse. The level of the mitral valve ring is shown by the **two black arrows.** The mitral valve leaflets lie within the left ventricle in systole. **Center,** mild mitral valve prolapse. The level of the mitral valve ring is depicted by the **two black arrows.** The anterior mitral valve leaflet lies just within the left atrium in systole. **Bottom,** severe mitral valve prolapse. The level of the mitral valve ring is shown by the **two black arrows.** Both the anterior and posterior mitral valve leaflets are situated well within the left atrium in systole. L = left; R = right; RA = right atrium; RV = right ventricle; other abbreviations as in Figure 4.

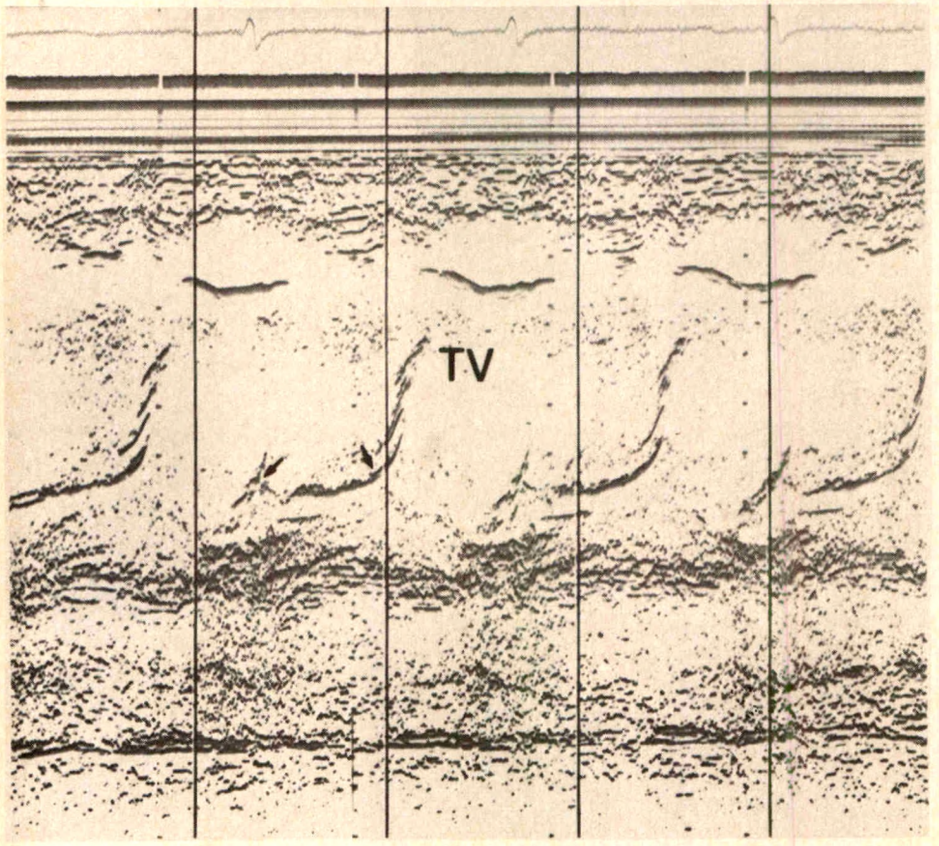


FIGURE 7. M mode echocardiographic tricuspid valve (TV). The **black arrow** de the tricuspid valve leaflet during systol holosystolic hammocking compatible wi of tricuspid valve prolapse.

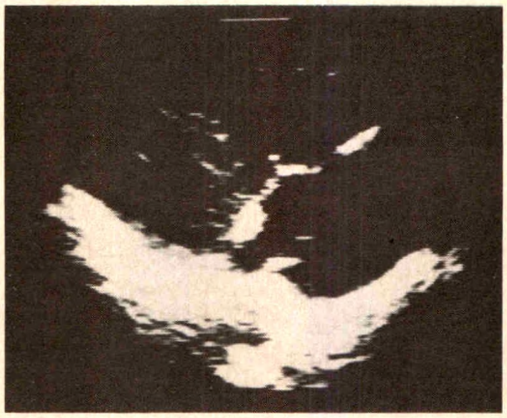
lets were at the level of the mitral valve ring with the leaflets bowed or prolapsed just toward the left atrium. Severe mitral valve prolapse was defined when both the coaptation point and the mitral leaflets were prolapsed toward the left atrium well below the level of the mitral valve ring. Moderate mitral valve prolapse was defined as a condition between mild and severe prolapse (Fig. 6). Severe mitral valve prolapse was easily identified equally with either view whereas in moderate mitral valve prolapse, the anterior mitral valve leaflet was more consistently identified with the apical view. In mild prolapse, the anterior and posterior leaflets were more consistently identified with the apical view ($p < 0.05$). For example, 8 patients of the 105 patients did have a moderate degree of mitral valve prolapse of the anterior leaflet in the apical view that was not detected in the longitudinal left ventricular view. In the 21 patients with mild mitral valve prolapse, the superiority of the apical view for detection of anterior leaflet prolapse was quite striking; 18 of 18 patients were detected with this view whereas only 2 of the 18 were detected with the left ventricular longitudinal view ($p < 0.05$). Ninety-nine of the 105 patients had M mode echocardiograms available for review, and 8 (8 percent) of the 99 had no evidence of mitral valve prolapse on M mode echocardiography.

Prolapse of the Tricuspid and Aortic Valves

Tricuspid Valve Prolapse

Two dimensional echocardiography: The presence of tricuspid valve prolapse has been sought using either pathologic or angiographic studies, and its prevalence rate in selected patients with mitral valve prolapse ranges from 21 to 52 percent.[37,87–90] In light of the bias in selection of patients for pathologic evaluation and the technical difficulties of right ventricular angiography, M mode echocardiography has been applied as a means of detecting tricuspid valve prolapse. In the largest series, Werner et al.[91] found 21 percent of their 53 patients to have concomitant mitral and tricuspid valve prolapse (Fig. 7). Because M mode echocardiographic imaging of the tricuspid valve is inconsistent and usually visualizes only the anterior tricuspid leaflet, we employed[92] the technique of two dimensional echocardiography in 64 patients who had definite mitral valve prolapse on two dimensional echocardiography.[84] Each of these patients had an adequately visualized tricuspid valve in either the right ventricular inflow longitudinal view or the apical view.[85,93] We have found that both of these views can be successfully obtained in 67 percent of patients.

Tricuspid valve motion characteristics in these patients with mitral valve prolapse were compared with those in a control group consisting of patients with a variety of cardiac diagnoses who had normal mitral valve closure pattern on left ventricular angiography and two dimensional echocardiography. None of the control population demonstrated displacement of the anterior or septal leaflets of the tricuspid valve toward



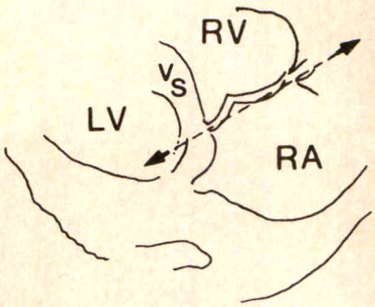


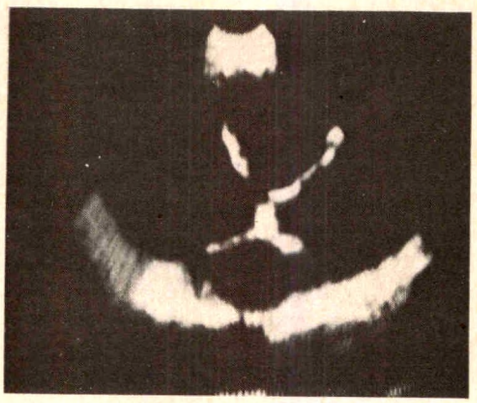
FIGURE 8. Normal tricuspid valve. Right ventricular long axis view. The level of the tricuspid valve anulus is depicted by the **two black arrows.** The tricuspid valve leaflets lie within the right ventricle. Abbreviations as in Figures 4 and 6.

the right atrium during systole (Fig. 8). Thirty-one (48 percent) of 64 of patients with mitral valve prolapse demonstrated tricuspid leaflet prolapse in which the anterior or septal leaflets, or both, of the tricuspid valve in systole prolapsed superior to the tricuspid atrioventricular ring into the right atrium (Fig. 9). Twenty-nine of the 32 had tricuspid valve prolapse of both visualized leaflets (anterior and septal). The right ventricular inflow tract view appeared to demonstrate tricuspid valve prolapse more easily than the apical four chamber view in our study.

Among those patients with tricuspid valve prolapse a more severe form of mitral valve prolapse was prevalent. Patients with both tricuspid and mitral valve prolapse also tended to be older and to have more frequent symptoms of chest pain, palpitations and dizziness and more of them had systolic clicks. Thus, these two dimensional echocardiographic data suggest that the prevalence rate of tricuspid valve prolapse may be as high as 50 percent in patients with mitral valve prolapse, which is similar to the prevalence rate demonstrated by angiographic or pathologic studies.[89] Isolated tricuspid valve prolapse has not been documented.[9,91] The high prevalence rate of tricuspid valve prolapse in patients with mitral valve prolapse suggests that the myxomatous degeneration responsible for this syndrome appears not to be isolated to just one of the atrioventricular valves and theoretically could involve all the cardiac valve tissue.

Tricuspid regurgitation detected with contrast two dimensional echocardiography: In a subsequent analysis we evaluated 45 patients with contrast two dimensional echocardiography to assess the prevalence of tricuspid regurgitation in patients with tricuspid valve prolapse. Four groups were formed: Group A, 10 healthy control subjects with normal cardiac catheterization findings; Group B, 10 patients with classic clinical evidence of tricuspid regurgitation; Group C, 10 patients with two dimensional echocardiographic evidence of mitral valve prolapse[84] without tricuspid valve prolapse; and Group D, 15 patients with both mitral and tricuspid valve prolapse on two dimensional echocardiography. Tricuspid regurgitation was sought for in each group by using the subxiphoid echocardiographic approach with peripheral venous injection of saline solution.

Tricuspid regurgitation is difficult to define by physical examination,[94] and its angiographic definition is obscured by the necessity of placing a catheter across the tricuspid valve to perform right ventricular angiography. Recently, contrast two dimensional echocardiography was demonstrated to be a highly sensitive and



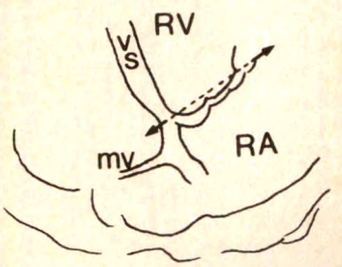


FIGURE 9. Tricuspid valve prolapse. Right ventricular long axis view. The tricuspid leaflets in systole lie within the right atrium and have a scalloped appearance compatible with prolapse. The **two black arrows** point to the level of the tricuspid ring. MV = anterior mitral valve leaflets; other abbreviations as before.

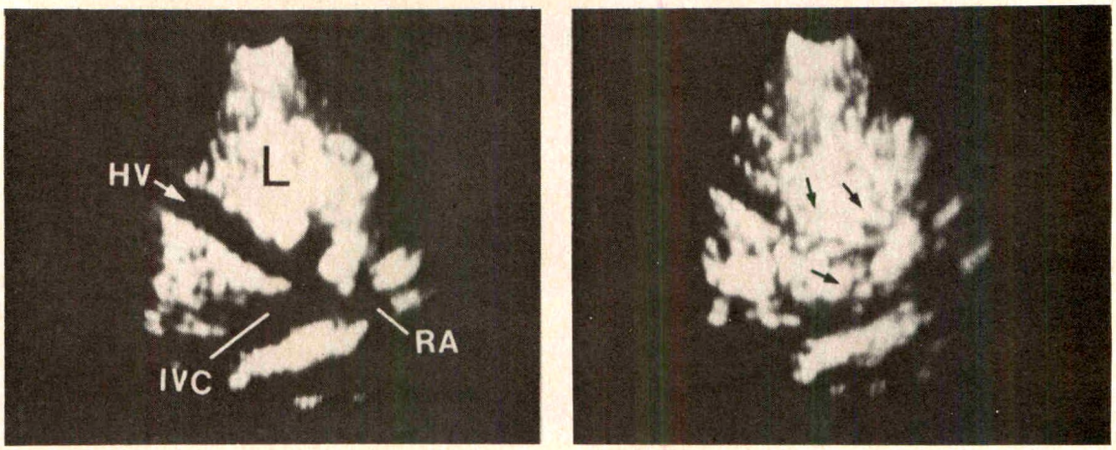


FIGURE 10. Tricuspid regurgitation. **Left,** subxiphoid view of the liver (L), inferior vena cava (IVC), hepatic vein (HV) and right atrium (RA). **Right,** microcavitations are present in the inferior vena cava and hepatic veins (**arrows**) after a peripheral venous injection of saline solution in a patient with tricuspid valve prolapse. These microcavitations persisted for three cardiac cycles and suggest the presence of tricuspid regurgitation.

specific technique for identifying tricuspid regurgitation.[95] Strict criteria for tricuspid regurgitation were sought for in which the microcavitations need not be present only in the inferior vena cava from a peripheral upper limb injection of saline solution but also had to be in the hepatic veins for at least three consecutive cardiac cycles. With use of this strict definition, echocardiographically defined tricuspid regurgitation was observed in none of the patients in Group A or C, in all patients in Group B and in 6 (40 percent) of the 15 patients in Group D (Fig. 10).

Thus, it appears that patients with both tricuspid and mitral valve prolapse have a high prevalence rate (40 percent) of tricuspid regurgitation as detected with the very sensitive technique of contrast two dimensional echocardiography. The high prevalence rate of tricuspid regurgitation in patients with tricuspid valve prolapse is similar to the high prevalence rate (50 to 65 percent) of systolic murmurs and angiographically proved mitral regurgitation in patients with the mitral valve prolapse syndrome.[30] Of course, the finding of the high prevalence rate of tricuspid regurgitation in patients with tricuspid valve prolapse as defined solely with two dimensional echocardiography does suggest that this technique is identifying an abnormal tricuspid valve, which is part of a more extensive spectrum of cardiac skeletal myxomatous degeneration.

Aortic Valve Prolapse

M mode echocardiography: The identification by Sahn et al.[83] of the association of aortic root dilatation with mitral valve prolapse in 85 percent of their patients suggested the possibility that myxomatous degeneration may involve not just the tricuspid and mitral valves, but also the aortic valve. Aortic valve prolapse has previously been demonstrated in surgical and pathologic studies.[12,96,97] M mode echocardiography as a means of detecting aortic valve prolapse has been suggested by the presence of diastolic aortic leaflet fluttering.[98] Rippe et al.[99] noted that a marked aortic valve excursion pattern on M mode echocardiography may suggest aortic valve prolapse. Because the aortic valve anulus is smaller than the mitral anulus and the aortic cusp less voluminous and less echo-reflective than the atrioventricular valve anulus or leaflet, noninvasive identification of aortic valve prolapse on M mode echocardiography should be difficult.

Two dimensional echocardiography: This method provides real time evaluation of the aortic valve, and we[100] therefore applied this technique to a group of 112 patients with mitral valve prolapse defined with two dimensional echocardiographic criteria[84] to analyze aortic valve motion characteristics.[86] In 14 control subjects with normal cardiac catheterization findings two dimensional echocardiography revealed that the aortic valve leaflets were faint echo reflectors with symmetric cusps in which the cusps and coaptation points did not display any downward or prolapsing motion toward the left ventricular outflow tract in diastole (Fig. 11). Of the 112 patients with mitral valve prolapse studied, the aortic valve was successfully imaged for detailed analysis in 77. In 60 of these 77 (78 percent) with a mean age of 38 ± 18 years two dimensional echocardiography revealed aortic valve morphologic and motion characteristics to be identical to that found in control subjects. In the remaining 17 patients with a mean age of 32 ± 21 years (65 percent female) there was a downward displacement of prolapsing motion of the aortic valve cusp during diastole toward the left ventricular outflow tract (Fig. 12). There was an increased echo reflection from the cusp tissue in 16 of these 17 and in 6 the cusp size was asymmetric producing eccentricity of the coaptation point. In all six of these patients three aortic cusps were seen in the short

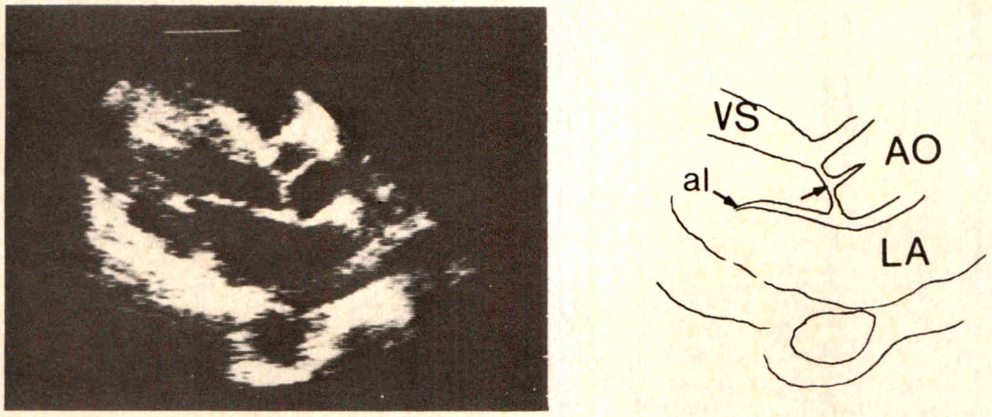


FIGURE 11. Normal aortic valve. Left ventricular long axis view depicting the aortic valve in diastole. The tip of the **black arrow** demonstrates the coaptation point of the right and noncoronary cusps, which lie within the aorta in diastole; the coaptation point appears to be in the mid aortic root position. Abbreviations as in Figure 4.

axis view. The aortic root size was normal in all control subjects and in all 60 of the patients with mitral valve prolapse without aortic valve prolapse. However, the aortic root was enlarged on M mode echocardiography in 6 of the 17 patients with both aortic valve and mitral valve prolapse. Aortic insufficiency was present in 4 of these 17 patients but in none of the 60 patients with mitral valve prolapse alone ($p < 0.01$).

Thus, real time two dimensional visualization of the aortic valve in which superior and inferior directions of aortic valve tissue can be visualized provides noninvasive presurgical identification of aortic valve prolapse. M mode echocardiographic features of increased aortic valve reflections, eccentricity of the diastolic closure line, aortic root enlargement and the presence of fluttering of the anterior mitral leaflet are all suggestive of the possibility of coexisting aortic valve prolapse in patients with mitral valve prolapse.

Conclusion: Two dimensional echocardiography may provide the means for a specific and sensitive evaluation of mitral, tricuspid and aortic valve motion characteristics and should be considered the diagnostic standard by which the syndrome characterized by prolapse of a cardiac valve is defined. Clearly, the use of physical examination, angiography or M mode echocardiography has important limitations in reference to echocardiography. Without the means to identify myxomatous degeneration in cardiac tissue prior to necropsy, it appears that two dimensional echocardiography may be the best "gold standard" for detection of prolapsed mitral, tricuspid or aortic valve leaflets. Natural history, prevalence, genetic transmission, treatment course and, more importantly, persons who are more prone to complications can now rationally be identified among patients with this common and perplexing cardiac syndrome.



FIGURE 12. Aortic valve prolapse. Left ventricular long axis view. The **black arrow** points to an asymmetric increased echo-reflective right coronary cusp that in diastole is situated in the left ventricular outflow tract at the mitral valve level. Abbreviations as in Figure 4.

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Echocardiographic Detection of Coronary Artery Disease

Detection of Effects of Ischemia on Regional Myocardial Wall Motion and Visualization of Left Main Coronary Artery Disease

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M mode and cross-sectional echocardiographic studies at rest have been used to detect regional left ventricular wall motion abnormalities as a sign of hemodynamically significant coronary artery disease. These techniques have proved to be fairly specific but not highly sensitive. Detection of new regional wall motion abnormalities with cross-sectional echocardiography during exercise appeared practical in 80 percent of patients in preliminary studies; the finding of such abnormalities is highly specific for the presence of coronary artery disease and, with this approach, the sensitivity of echocardiography is improved. Thus, patients with anatomically severe coronary artery disease on angiography may not manifest an echocardiographic abnormality in regional wall motion even during exercise. The direct noninvasive detection of the left main coronary artery in up to 90 percent of patients studied with cross-sectional echocardiography using the short axis or apical approach, or both, has been well defined. A high sensitivity and specificity of detecting anatomically severe left main coronary artery disease using the criteria of both luminal impingement and the presence of high intensity echoes have been confirmed. Further advances in imaging techniques may allow for better definition of the coronary arterial tree.

Cross-sectional echocardiography is the first technique providing noninvasive visualization of the coronary arteries in man.[1–11] In fact, the technique has been reported[8] to permit accurate prospective identification of obstructive disease of the left main coronary artery. Not only can echocardiography *directly* visualize the diseased coronary artery, but also it can *indirectly* detect the effects on the left ventricle of acute and chronic ischemia caused by coronary artery disease. Forty-five years ago Tennant and Wiggers[12] demonstrated by direct observation of the heart, regional myocardial wall motion abnormalities during ischemia induced by acute coronary arterial ligation in the open chest dog. Recently, the echocardiographic identification of segmental regional left ventricular wall motion abnormalities has been extensively studied as a means of predicting the presence of hemodynamically significant coronary artery disease associated with ischemia or myocardial infarction, or both.[13–28] In addition to affecting regional wall motion, coronary artery disease may change the shape of the ventricle as well as its global performance, and these alterations may be used as indirect markers of the presence of coronary artery disease. This report will not consider such alterations but will examine in detail attempts to detect the effects of ischemia on regional myocardial wall motion at rest or during exercise, or both, and to visualize directly the left main coronary artery.

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Regional Wall Motion Abnormalities in the Detection of Coronary Artery Disease

M Mode Echocardiographic Studies at Rest

Abnormal septal and posterior wall motion: In the early 1970s Inoue,[13] Stefan[14] and Kerber[16,23] and their co-workers demonstrated in open chest dogs that acute ligation of the left anterior descending or left circumflex coronary artery could induce an immediate decrease in motion of the associated regional myocardial wall as well as a decrease in its velocity, excursion and thickening during systole. During the same period, data on human subjects were reported. Dortimer et al.[24] studied 56 patients with a history of angina pectoris without prior myocardial infarction and found that 28 (80 percent) of 35 patients with disease of the left anterior descending coronary artery had diminished interventricular septal motion, whereas 14 (52 percent) of 27 with disease of the posterior coronary vessels had diminished posterior wall motion. Similar findings (Fig. 1) were reported by other workers. Gordon et al.[25] studied 26 patients with left anterior descending coronary artery disease and found that 12 (46 percent) had abnormal septal motion at rest (systolic excursion less than 2 mm). Joffe et al.[26] demonstrated that among 77 patients only 2 of 38 without left anterior descending coronary artery disease had abnormal septal motion at rest compared with 17 of 39 patients with such disease. Thus, the presence of an M mode echocardiographic segmental ventricular septal motion abnormality at rest was quite specific for the presence of left anterior descending coronary artery disease. However, this observation was not highly sensitive because only about half of the patients with such disease had abnormal regional wall motion at rest.

Correlation with angiographic findings: Observed changes in segmental wall motion at rest on M mode echocardiography have been correlated with anatomic location of coronary artery disease. Jacobs et al.[15] studied 48 patients undergoing selective coronary angiography and left ventricular cineangiography for the evaluation of chest pain. Ventricular septal wall motion and posterior left ventricular wall motion were normal in patients found to be free of coronary artery disease but either or both were abnormal in all but one of those subjects manifesting left ventricular asynergy on angiography. However, the correlation was not invariably direct. In their report, 17 patients with significant coronary artery disease manifested no abnormality in wall motion on left ventricular cineangiography although 8 manifested such abnormalities on echocardiography. In addition, all patients with abnormal ventricular septal motion had significant obstruction of the left anterior descending coronary artery, but 8 patients with significant disease of this artery had normal septal motion on M mode echocardiography.

Correlation with myocardial perfusion studies: The mechanism of abnormal regional wall motion has been studied by investigators using myocardial perfusion techniques. Kolibash et al.[28] demonstrated that 12

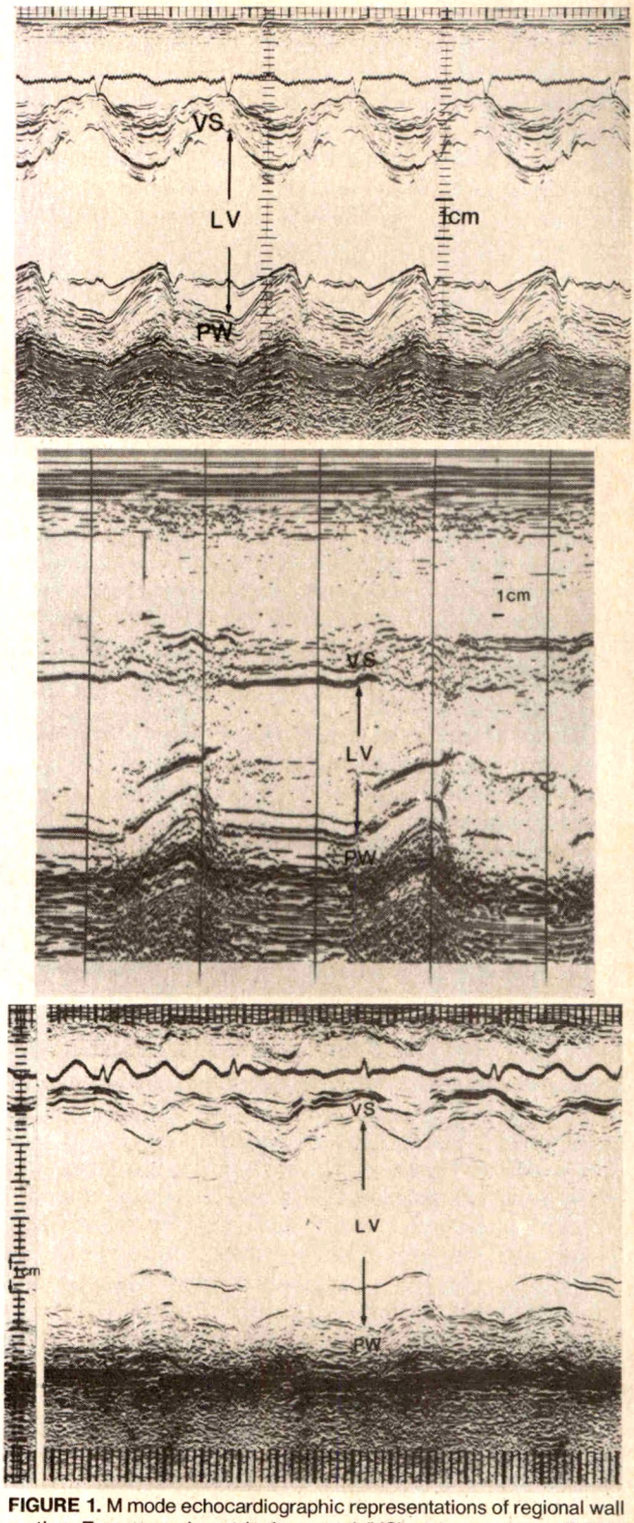


FIGURE 1. M mode echocardiographic representations of regional wall motion. **Top,** normal ventricular septal (VS) and posterior wall (PW) motion. The left ventricular cavity (LV) is depicted as well as a 1 cm marker. **Center,** normal posterior wall motion in a patient with a nondilated left ventricular (LV) cavity with thinning and marked hypokinesia of the ventricular septum (VS). This patient had an anteroseptal myocardial infarction due to left anterior descending coronary artery disease. **Bottom,** patient with a borderline left ventricular (LV) cavity size and normal ventricular septal (VS) motion but markedly hypokinetic posterior wall (PW) motion due to inferoposterior myocardial infarction caused by right coronary arterial obstruction.

of 25 patients with critical (greater than 70 percent) obstruction of the left anterior descending coronary artery had abnormal echocardiographic septal motion, whereas 13 had normal motion. When studied with intracoronary injections of radioactive macroaggregated albumin particles, 10 of the 12 patients with abnormal septal motion had absent septal perfusion at rest, whereas only 2 of the 13 patients with normal septal motion had abnormal septal perfusion. These investigators concluded that in patients with severe stenosis of the left anterior descending coronary artery the presence of abnormal septal motion on echocardiography strongly suggests marked abnormal septal perfusion as the cause of the wall motion abnormality.

Kerber et al.[19] demonstrated that decreased myocardial perfusion (determined with radioactive-labeled microspheres) caused by increasing coronary arterial constriction correlated with segmental wall motion abnormality in the dog. However, normal myocardial perfusion in nonischemic areas was at times associated with regional wall motion abnormalities that may have been caused either by transient undetected ischemia or by passive alterations in the motion of normal regional wall motion areas due to severe dyskinesia of adjacent ischemic myocardium.

Other factors producing abnormal wall motion: Dortimer et al.[24] pointed out that ventriculography only demonstrates a shadow of the circumferential rim of endocardium and that considerable amounts of endocardium are not projected by this technique. It is therefore theoretically possible that the echocardiographic beam may detect small areas of hypokinesia on the left ventricular endocardial surface that are not seen in the angiographic silhouette. This finding was not uncommon because among 48 patients studied, 12 (25 percent) had abnormal wall motion on echocardiography but no abnormality on ventriculography. Echocardiographically detected abnormal regional wall motion should not always be equated with ischemia induced by coronary artery disease. Corya et al.[21,27] demonstrated that regional wall motion abnormalities on M mode echocardiography may be caused not only by such ischemia, but also by motion of the entire heart within the chest, abnormal electrical conduction, relative diastolic volume overload of the right and left ventricles (such as that seen in atrial septal defect) and ischemic conditions induced by noncoronary artery diseases such as idiopathic congestive cardiomyopathy. Conduction abnormalities are usually distinguished by the electrocardiogram, relative volume increases by associated right ventricular volume overload, and other causes of ischemia such as congestive cardiomyopathy by lack of segmental abnormality often typical of patients with coronary artery disease.

In coronary artery disease, usually one area of the left ventricle will have good regional wall motion even in the presence of advanced disease with congestive heart failure, whereas in congestive cardiomyopathy diffuse regional wall motion abnormalities are usually, but not invariably, seen. Corya et al.[27] demonstrated that both septal and posterior left ventricular wall motion were markedly diminished in 9 of 10 patients with idiopathic congestive cardiomyopathy but in only 2 of 27 patients with coronary artery disease.

Limitations of M mode echocardiography: Limitations of M mode recordings in the detection of regional wall motion abnormalities have been well defined.[22] The "ice-pick" view of M mode echocardiography does not allow for simultaneous comparative evaluation of multiple regional wall motion changes or for evaluation of many areas of the ventricle. For example, the left ventricular apex is rarely well examined by M mode echocardiography. Thus, cross-sectional echocardiography has a theoretical advantage not only in providing multiple tomographic views of the left ventricle but also in determining ventricular shape and function.

Myocardial infarction: M mode echocardiographic studies in patients with acute myocardial infarction will not be discussed in this review. In general, abnormal regional wall motion corresponds well to the electrocardiographic site of infarction, and abnormal left ventricular internal dimension and mitral valve closure abnormalities correlate with hospital mortality.[20,21]

Cross-Sectional Echocardiography

In the open chest dog, cross-sectional echocardiography has been applied to detect noninvasively the immediate ventricular wall motion abnormalities that occur during experimental myocardial infarction.[29,30] The quality of the images is excellent and allows for quantification of endocardial motion as well as echocardiographic and electrocardiographic correlations (Fig. 2).[29,30]

Correlation with contrast angiography: To date, few clinical studies have analyzed the correlation between regional wall motion abnormality as assessed with cross-sectional echocardiography and left ventricular cineangiography. Kisslo et al.[31] reported in 1977 on an analysis of 525 regional wall motion studies in 105 patients undergoing cardiac catheterization; 430 studies (82 percent) were adequate for analysis. Ventricular wall motion detected with real time phased array echocardiography in the anterolateral, posterolateral, apical, septal and posterior regions was well correlated with left ventricular cineangiographic data. However, 55 of the 430 regions had discrepant findings in this comparison; reasons for the discrepancy were established for 54 of these. Of the 34 discrepancies attributed to echocardiography, 10 were due to observer error, 19 to inadequate visualization of echocardiographic targets that were previously judged as adequate, 4 to tangential angulation of the transducer through the short axis resulting in distortion of the wall movement; 1 was unexplained. Of the 15 discrepancies attributed to angiography, the majority (13) were due to superimposition of abnormally contracting wall regions over the normally contracting portions of the ventricle and 2 were caused by observer error. Six discrepancies were judged "indeterminate" because they could not be attributed to either imaging technique. This category included unre-

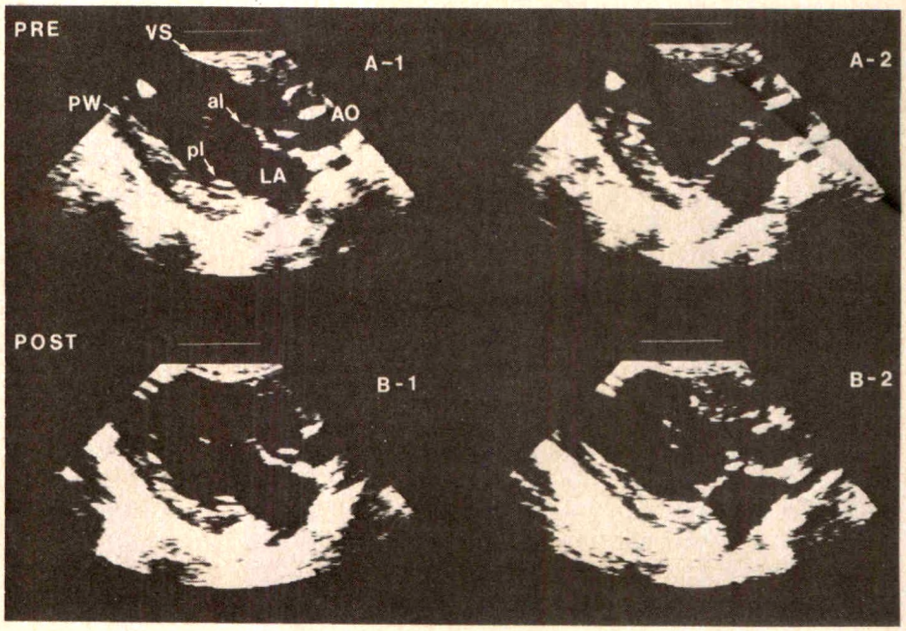


FIGURE 2. Cross-sectional echocardiographic left ventricular long axis views from an open chest dog. **A-1 and A-2** represent diastole and systole, respectively, before (PRE) ligation of the posterior coronary artery. The posterior wall motion during systole (A-2) is well demonstrated. **B-1 and B-2** represent diastole and systole after (POST) ligation of the posterior coronary artery. During diastole (B-1) the left ventricle is larger in internal diameter, and in systole (B-2) the posterior wall is akinetic. The left ventricular internal dimension is larger in B-2 than in A-2, suggesting a decrease in left ventricular ejection fraction. al = anterior mitral valve leaflet; AO = aorta; LA = left atrium; pl = posterior mitral valve leaflet; PW = posterior wall; VS = ventricular septum.

solved disagreements between interpretations (echographic to angiographic orientation [two cases] and definition of asynergy [four cases]). Discrepancies due to observer error and inadequate target visualization were most frequently encountered in the interpretation of apical wall motion, whereas problems experienced with the ventricular silhouette on angiography were most frequently encountered in analysis of ventricular septal motion. Kisslo et al. concluded that at least 50 percent of the endocardium in any one wall region must be visualized throughout the cardiac cycle on echocardiography to permit reliable prediction of the presence or absence of wall motion abnormalities on angiography. In their study, the regions most readily visualized with echocardiography were the ventricular septum and posterior wall; the most difficult region to visualize was the ventricular apex.

Echocardiography requires concentrated attention to proper technique to avoid error in analysis because the heart is in constant motion and, as a three-dimensional target, it rotates in and out of the ultrasonic beam during the cardiac cycle. Tangential imaging may distort the normal ventricular configuration and, thus, wall motion and observer error may result from poor visualization of the majority of endocardium in any particular tomographic view.

Of the errors attributable to angiographic detection, paramount was the superimposition of the silhouette of an abnormally contracted wall segment over one that was normal. Also, the ventricular wall surfaces may be inaccessible during left ventricular cineangiography because the motion detected by this method is seen along the borders of the ventricular silhouette. Because angiography is invasive, its application is limited to a relatively small number of patients compared with those who can be subjected to cross-sectional echocardiography.

Myocardial infarction: Cross-sectional echocardiography has been applied to patients with myocardial infarction. Heger et al.[32] demonstrated that the method provided a useful and accurate spatial orientation in the detection of left ventricular wall motion abnormalities during an acute myocardial infarction. Likewise, its use in detecting abnormalities in ventricular geometry and function has been explored and will not be considered in detail in this report. One major limitation of cross-sectional echocardiography is the proportion of patients in whom this technique images the endocardium well enough for adequate analysis. For example, in the study of Heger et al.,[32] 7 (16 percent) of 44 patients entered did not have adequate cross-sectional echocardiograms visualizing all nine myocardial segments used in analysis.

M Mode and Cross-Sectional Echocardiographic Studies During Exercise

It is not uncommon to observe normal left ventricular function at rest even in the presence of severe coronary artery disease. In patients with such findings, delivery of oxygenated blood to the myocardium due to obstructed coronary arteries is decreased but sufficient to supply myocardial needs at rest. However, during exercise ischemia may be produced as oxygen demand increases. New regional wall motion abnormalities during exercise-induced ischemia have been demonstrated with left ventricular cineangiography[33] and with cardiac nuclear imaging techniques.[34] Studies during acute coronary arterial ligation[29,30] demonstrated that with the onset of ischemia rapid deterioration of regional wall motion, including thickening and shortening

functions, occurred even before S-T segment changes were evident; these mechanical alterations were reversible on release of the coronary ligature.

M mode echocardiography during exercise: Studies in human beings using M mode echocardiography during exercise have been reported. Mason et al.[35] examined changes in regional wall motion in 54 men (mean age 51 ± 18 years) with adequate resting echocardiograms; however, only 24 (45 percent) had exercise echocardiograms adequate for analysis. Changes in regional wall thickening and left ventricular cavity dimension during exercise were evaluated. A decrease in regional wall thickening during exercise appeared to be a sensitive and specific indicator of the presence of significant coronary artery disease because an abnormal thickening occurred during exercise in only 1 (5 percent) of 22 normally perfused segments, whereas systolic thickening decreased in 19 (86 percent) of 22 abnormally perfused segments. Eleven of these patients had a positive exercise test; two had prior myocardial infarction. During exercise; the percent shortening of the left ventricular cavity dimension increased in 10 of 11 normal subjects, but decreased in 12 of 13 patients with coronary artery disease. Thus, M mode echocardiographic findings during exercise appear to differentiate patients with and without coronary artery disease. However, the limitations of this study include lack of an adequate number of normal subjects and a preponderance of patients with severe coronary artery disease. Among the 13 patients with coronary artery disease in this study, 9 had three vessel, 3 had two vessel, and only 1 had one vessel involvement.

Exercise protocols used during echocardiographic studies rely on the supine position rather than on the upright position common to the standard exercise test on the treadmill or bicycle. The supine position is adequate to induce ischemia because the patient reaches a higher heart rate and systolic blood pressure for a given level of oxygen consumption even in comparison with the upright position.[36]

The greatest limitation of the M mode echocardiographic exercise study is the difficulty of obtaining high quality echocardiograms during exercise. Among its advantages are that it is the only technique in which precise dynamic changes in myocardial wall thickness in different regions of the heart can be evaluated. It is, of course, noninvasive, easily repeatable and inexpensive. Echocardiography does not alter the function of the ventricle as angiographic contrast dye may, and a large number of cardiac cycles before, during and after intervention can be studied. Compared with stress radionuclide angiography, echocardiography follows instantaneous events rather than combining several cardiac cycles and, of course, it imposes no radiation exposure. Echocardiography can evaluate changes in wall thickening as well as endocardial motion, which cannot be assessed with gated blood pool scanning techniques.

Cross-sectional echocardiography: Cross-sectional echocardiography in the detection of regional wall abnormalities provides better visual orientation than is possible with the M mode echocardiographic "ice pick" view, but this use has only recently been explored. Wann and co-workers,[37] using cross-sectional echocardiography performed at rest and during supine bicycle exercise, studied 28 patients with classic angina pectoris or prior myocardial infarction, or both, who were undergoing cineangiography. Technically adequate exercise echocardiograms were obtained in 20 (71 percent) of the 28 patients and, although many of the cross-sectional echocardiograms performed during exercise were of a lesser quality than that of studies performed at rest, they were sufficiently good to be diagnostic. The investigators had the greatest success with the apical echocardiographic window, since only 11 (39 percent) of the 28 patients studied had adequate parasternal visualization. Of the 20 patients with adequate cross-sectional echocardiograms, new regional wall motion abnormalities were detected in 10; 8 of the 10 experienced typical angina pectoris during exercise. Exercise-induced abnormal myocardial wall motion that was not detected at rest could be seen to normalize gradually during the recovery period. Six of these 10 patients had stenosis of coronary arteries supplying areas of the heart corresponding to the location of reversible wall motion abnormalities. Thallium-201 perfusion scanning showed that these patients also had reversible perfusion defects during exercise. Five of the other 10 patients without new regional wall motion abnormalities during exercise had coronary artery disease.

In a preliminary study, we[38] evaluated 20 consecutive patients undergoing coronary angiography using wide angle cross-sectional echocardiography at rest and during supine bicycle exercise. Eighteen (90 percent) of the 20 patients had endocardial echoes during exercise that were adequate for analysis. Sixteen of these 18 had angina pectoris and 6 had electrocardiographic evidence of prior myocardial infarction. In 10 patients cross-sectional echocardiographic regional wall motion was normal at rest and remained so during exercise. Seven of these 10 had coronary artery disease, although none of the 7 had prior myocardial infarction or abnormal findings on left ventricular cineangiography. New regional wall motion abnormalities on exercise cross-sectional echocardiography appeared in eight patients; all eight had a positive exercise test and seven had coronary artery disease, including six with three vessel and one with two vessel disease (Fig. 3). One patient did not have coronary artery disease but had an occult cardiomyopathy on angiography. The location of new exercise regional wall motion abnormalities correlated directly with the presence of major obstruction in the coronary arteries supplying that segment. Thus, exercise echocardiography can detect the presence of coronary artery disease with a high degree of specificity although the sensitivity of this technique may be limited.

Direct Visualization of the Coronary Arteries

Weyman et al.[1] was the first to report (in 1976) direct visualization of the left main coronary artery using

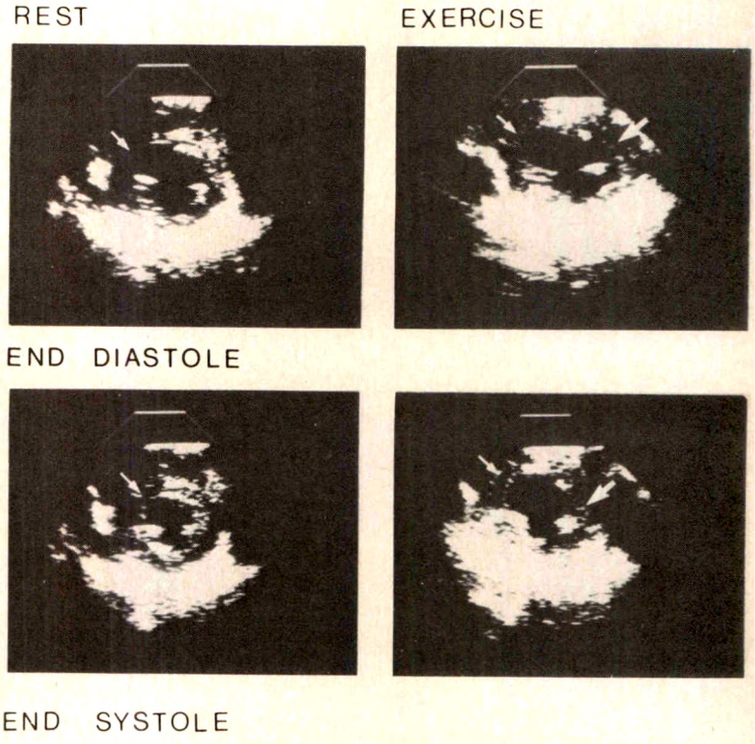


FIGURE 3. Cross-sectional echocardiographic short axis view of the left ventricular cavity at the level of the papillary muscle recorded at rest and during exercise. **Left panels** demonstrate end-diastole and end-systole at rest. The **white arrow** points to the region of the ventricular septum, which during systole at rest has excellent inward motion. **Right panels** demonstrate end-diastole and end-systole during exercise. The end-diastolic exercise frame (**upper panel**) demonstrates a larger left ventricular internal cavity dimension. The **small white arrow** points to the ventricular septum and the **large white arrow** to the anterolateral wall. During systole (**lower right panel**) the ventricular septum appears to have become akinetic (**small white arrow**), whereas the anterolateral left ventricular wall (**large white arrow**) maintains normal motion. The end-systolic left ventricular diameter appears to be larger during exercise than at rest, suggesting that the ejection fraction decreased during exercise.

cross-sectional echocardiography. Previously, visualization of this artery had been obtained only with coronary arteriography. It is well accepted that there is no historical or clinical feature specific for left main coronary artery disease, including a markedly positive treadmill test.[39–42] The importance of noninvasive diagnosis of such disease stems from the evidence that coronary bypass surgery prolongs life in patients who are symptomatic with the disease. Therefore, the prompt identification of left main coronary artery disease in patients with ischemic cardiac symptoms becomes an important therapeutic challenge to the cardiologist.[42–44] In addition, the detection before cardiac catheterization of left main coronary artery disease may minimize the risk of angiography in such patients.[45]

Visualization of the normal left main coronary artery: Weyman et al.[1] evaluated the left main coronary artery in 15 apparently normal subjects and in 15 patients with coronary artery disease who had a normal left main coronary artery on angiography. Three patients with 75 percent obstruction of the left main coronary artery and one patient with a large aneurysm of its distal portion were also studied. Identification of the left main coronary artery was performed using a 30° sector scanner and the short axis view of the great vessels (Fig. 4). Because this artery normally lies in a fixed anatomic position in reference to the left ventricle and great vessels, the short axis view of the level of the great vessels was utilized. The probe was swept in a superoinferior arc to locate the superior margin of the left ventricle and the descending portion of the pulmonary artery. These represented the upper and lower limits of the area in which the left main coronary artery was found. During the sweep a relatively dense mass of echoes originating along the left inferior border of the aorta and extending leftward beneath the right ventricular outflow tract could be visualized. The transducer was then rotated parallel to the short axis in an attempt to line up the plane of the ultrasonic beam more closely to the course of the left main coronary arterial segment. Fine changes in the plane of the cross-sectional scan were required to align the transducer sweep parallel to the long axis of the left main coronary artery. To confirm that the structure visualized was indeed the left main coronary artery, indocyanine green dye was in-

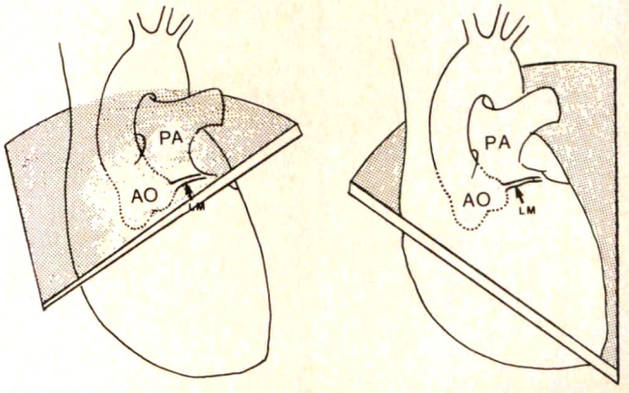


FIGURE 4. Left, schematic drawing of the short axis view of the great vessels (AO = aorta and PA = pulmonary artery) and the left main (LM) coronary artery. **Right,** schematic cross-sectional echocardiographic plane using the apical approach.

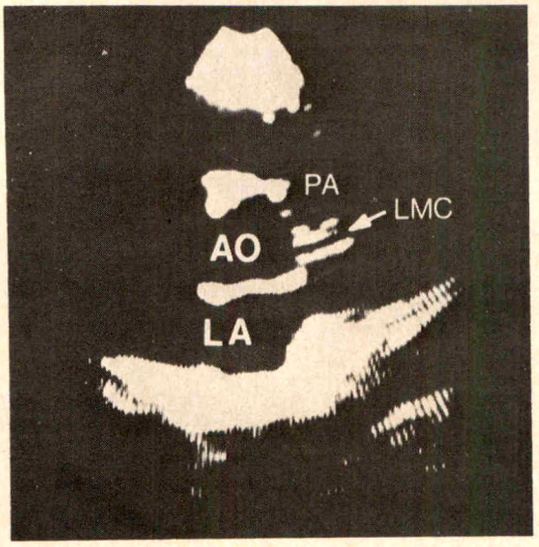


FIGURE 5. Cross-sectional echocardiographic view of the short axis at the great vessel level. The left main coronary (LMC) artery is depicted with its lumen in continuity with that of the aorta (AO). LA = left atrium; PA = pulmonary artery.

jected directly into this artery during cardiac catheterization in two patients and into the aortic root in the area of the left coronary ostium in one patient.

Figure 5 demonstrates a normal left main coronary artery detected with the short axis view and shows it to be an elongated funnel-shaped structure arising from the lateral margin of the aortic root with the coronary ostium in continuity with the aortic lumen. The left main coronary artery appears as two parallel sets of echoes arising from the vessel. The echo-free space between these two inner echoes represents the lumen.

Left main coronary disease: In each of the three patients with left main coronary artery disease studied by Weyman et al.[1] a luminal narrowing evident on echocardiography correlated with almost complete obliteration of the lumen demonstrated on angiography. An aneurysm of the left main coronary artery in one patient was also imaged with echocardiography. It is important that the origin of the artery from the aorta be imaged and that the continuity between the lumens of these two vessels be ensured in order to be certain that the left main coronary artery is being imaged. Several still frames were required to visualize the left main coronary artery because it moves in and out of the ultrasonic beam during the cardiac cycle.

Coronary arteries in mucocutaneous lymph node syndrome: Cross-sectional echocardiography has been used to evaluate the coronary arteries in infants and young children with the mucocutaneous lymph node syndrome.[4,5] This obscure syndrome is characterized by aneurysms of the coronary artery and myocardial infarction. Cross-sectional echocardiography may be used as a screening procedure for this syndrome to determine whether the left main coronary artery is aneurysmal. Yoshikawa et al.[4] in their study also demonstrated by the short axis view visualization of the ostium of the right as well as the left coronary artery. The left main coronary artery was visualized in 29 of their 37 subjects and the right coronary artery in 17. Fifteen patients had apparently normal coronary arteries without invasive studies; 17 had proved normal coronary arteries and 5 had a left coronary arterial aneurysm; in 1 patient the right coronary artery was seen to communicate with a right coronary aneurysm. The right coronary artery has also been demonstrated in children with the anomalous left coronary artery syndrome.[10]

Apical four chamber approach: Ogawa and coworkers[2,9] attempted to visualize the left main coronary artery by using the apical (four chamber) approach using phased array ultrasonography (Fig. 4). After the standard four chamber view was obtained, the transducer was placed at the cardiac apex while the patient was in the left lateral decubitus position and the echocardiographic beam was directed toward the base of the heart perpendicular to the plane of the ventricular and atrial septums. The transducer was initially angled slightly posteriorly so that the beam passed through the plane of the mitral and tricuspid valves and then was angled slightly anteriorly until the aorta and pulmonary artery were imaged and no mitral valve tissue was identified. The transducer position was then altered slightly clockwise with the increased rejection of low frequency echoes until the left main coronary artery was imaged as a parallel set of echoes with a lumen-free space contiguous with the lumen of the aorta (Fig. 6). Frame by frame review of videotape recordings after recording of the initial data was necessary because the left main coronary artery moves with each cardiac cycle. Visualization of the left main coronary artery was documented by a frame by frame analysis of the tip of a Judkins coronary arterial catheter passing from the aortic lumen to the structure that had previously been identified as the left main ostium. Careful control of echocardiographic gain and rejection was important in order to detect the left main coronary artery, whose lumen had to be in continuity with the aortic root, and the luminal pattern had to be demonstrated for at least three consecutive stop frames.

In the preliminary studies of Ogawa et al. three patients with left main coronary artery disease on cineangiography had the obstruction identified with the apical view of the cross-sectional echocardiogram as a disruption of the continuous echo-free luminal space. Thirty-five patients were then studied prospectively and 27 had adequate visualization of the left main coronary artery. Twenty-three of these 27 were judged to have a normal left main coronary artery on echocardiography and all had normal coronary angiographic findings. Of the four patients judged to have an abnormal left main coronary artery, two in fact did have left main coronary obstruction; one had an abnormally short left main artery with severe obstruction of the proximal left anterior descending coronary artery; and one had

a normal left main coronary artery and was considered to have a false positive echocardiographic study. Ogawa et al.[9] subsequently studied 30 patients using both the short axis and apical approaches to identify the left main coronary artery. In 16 (53 percent) of the 30 this artery was clearly imaged with the short axis approach; in 21 (70 percent) it was visualized with the apical approach and in 28 (93 percent) with either approach.

Other echocardiographic criteria of left main coronary disease: Chen et al.[8] evaluated other criteria for disease of the left main coronary artery. Because this artery may bend in its course and move with each heartbeat and thus simulate a break in the continuous luminal free space, markers other than disruption in the continuous echo lumen were considered for identification of the left main coronary artery. The potential use of asymmetric high intensity echoes in the walls of the left main coronary artery reflecting the presence of atherosclerotic lesions was explored. Increased echocardiographic density reflecting collagen buildup in the left ventricle after myocardial infaraction has been identified,[46] and Rogers et al.[47] presented preliminary data suggesting that high intensity echoes from the wall of the left main coronary artery may be a manifestation of atherosclerotic plaque in that vessel.

Chen et al.[8] studied 73 patients undergoing cardiac catheterization for symptomatic ischemic heart disease, 60 percent of whom were referred for coronary arterial surgery. Twenty-one patients (20 were men with a mean age of 59 ± 8 years) had left main coronary stenosis (50 percent or greater narrowing of luminal diameter). Fifty-two patients had a normal left main coronary ar-

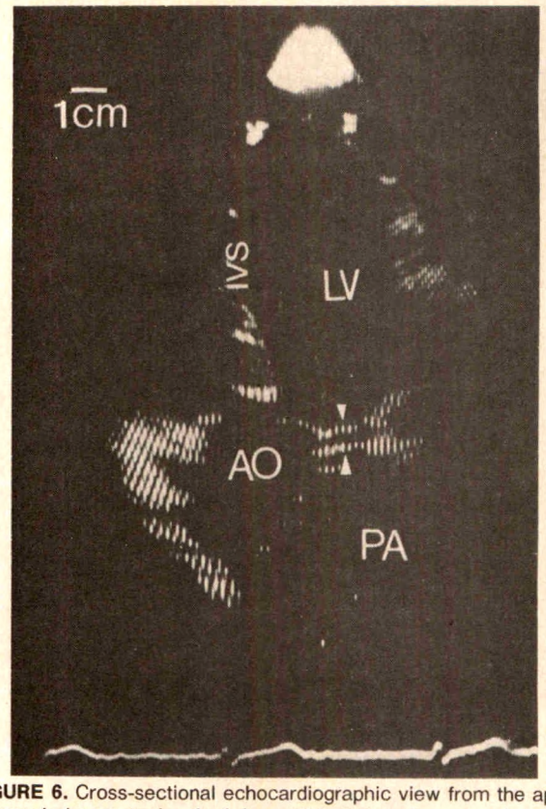


FIGURE 6. Cross-sectional echocardiographic view from the apical approach demonstrating the left ventricle (LV), pulmonary artery (PA), interventricular septum (IVS) and aorta (AO). A normal left main coronary artery is depicted (between the **two white markers**) arising from the aorta. The lumen of the artery is contiguous with that of the aorta.

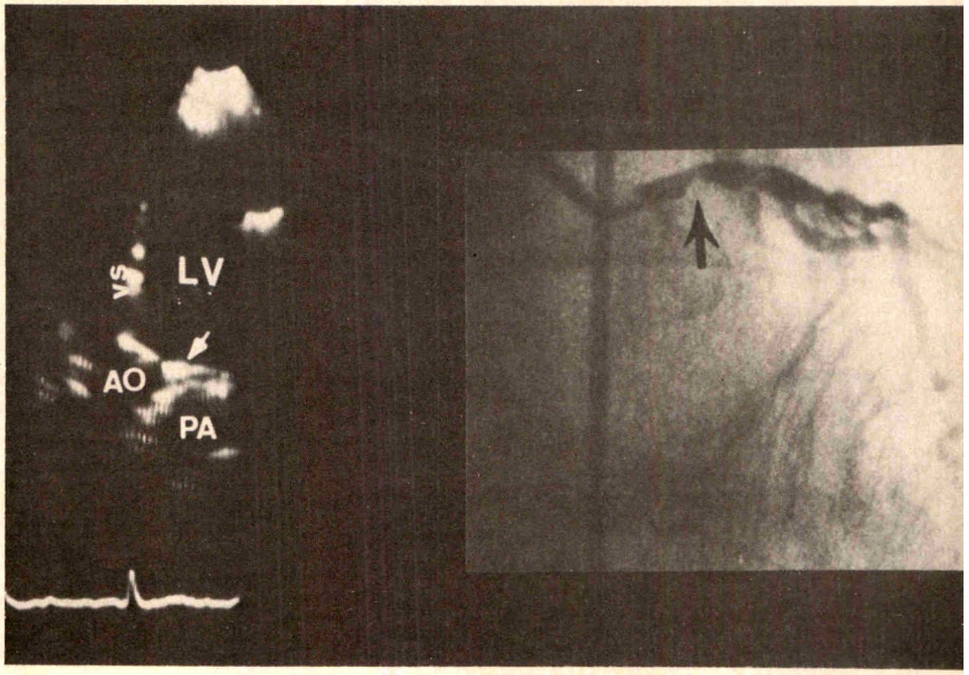


FIGURE 7. Left, the left main coronary artery (**arrow**) arises from the aorta and is bordered superiorly by the left ventricle (LV). The luminal space of the artery is interrupted in its proximal half and there is an asymmetric echo density in the arterial wall closest to the left ventricle. **Right,** the left main coronary angiogram from this patient demonstrates a major obstructing lesion (**arrow**) that correlates with the abnormality seen in the echocardiogram.

tery at cardiac catheterization and served as the control group. Forty-three of these were men with a mean age of 56 ± 9 years. In this study fluoroscopic evaluation for main coronary arterial calcification was not used.

In 36 (69 percent) of the 52 subjects with a normal left main coronary artery studied by Chen et al., adequate visualization of the artery was obtained. Failure to identify the left main coronary artery was due primarily to interference from lung or abnormal chest wall configurations preventing the detection of an adequate apical view. In addition, the presence of aortic valve calcification producing the confusing array of echo densities in the area of the left main coronary artery also revented visualization as would the presence of an aortic valve prosthesis.

Thirty-three of the 36 patients studied by Chen et al. with adequate visualization had normal symmetric echo densities rising from the walls of the left main coronary artery and a normal lumen without disruption. Three subjects had asymmetric high intensity echoes and thus had a false positive echocardiographic study, and two of these subjects had in addition, luminal irregularities on echocardiography. Thus, 34 (94 percent) of 36 patients with a normal left main coronary arteriogram demonstrated no luminal abnormalities throughout the artery's length on echocardiography. Of the 21 patients with left main coronary arterial obstruction on angiography, 16 (76 percent) had adequate echocardiographic studies for analysis. Nine of these 16 had luminal irregularities suggestive of coronary obstruction and 5 of these 9 had, in addition, asymmetric echo densities (Fig. 7). Three of the seven patients without luminal irregularities had only asymmetric high intensity echoes suggesting atherosclerotic obstruction. Four patients had no echocardiographic abnormalities and were considered to have a false negative study. In all four patients the left main coronary artery was unusually long with the lesion located distally just at the bifurcation point out of view of the left main artery as imaged by the echocardiogram. Thus, left main coronary artery disease was detected with the echocardiographic criteria of either asymmetric high intensity wall density or disruption of the arterial lumen in 12 (75 percent) of 16 patients. Similar data were reported by Rogers et al.[3]

Implications: Thus, cross-sectional echocardiography may visualize directly the left main coronary artery and predict obstructive disease with a high degree of specificity and sensitivity. Further, experience and improvements in echocardiography with more certain identification of the bifurcation point of the left main coronary artery will provide increasingly better results. To date, identification of specific left anterior descending and left circumflex coronary artery lesions has not been possible with any degree of reproducibility. With increasing interest in identifying those subjects with left main coronary artery disease, further studies of cross-sectional echocardiographic techniques and criteria aimed at the noninvasive evaluation of this problem are warranted.

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Exercise Radionuclide Imaging Approaches to Coronary Artery Disease

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Exercise thallium-201 myocardial imaging and exercise radionuclide angiography are the two techniques of nuclear cardiology most widely used for the diagnosis of coronary artery disease. Each of these tests provides information of diagnostic and functional value. The diagnostic accuracy and clinical utility of these two tests for the detection of coronary artery disease are compared. The strengths and weaknesses of each approach are discussed. A clinical approach to the detection and evaluation of coronary artery disease using these radionuclide exercise techniques is presented.

Exercise stress testing has long been used as a provocative maneuver for detecting coronary artery disease.[1–3] When current treadmill techniques were used and criteria for a positive test result and adequate stress testing (85 percent or greater predicted maximal heart rate) were evaluated, electrocardiography was reported[4] to be 60 to 64 percent sensitive and 89 to 93 percent specific for coronary artery disease. The diagnostic accuracy of the test is dependent on the level of stress achieved by the patient and the electrocardiographic criteria used for interpretation. Despite the reasonably high specificity of the electrocardiographic stress test, a positive test in the absence of chest pain is not specific. If the stress test is used for screening in a population with a small incidence of coronary artery disease, the number of false positive studies may be quite large.[4] Furthermore, several factors render the test difficult or impossible to interpret including (1) left or right ventricular hypertrophy, (2) intraventricular conduction delay or bundle branch block, (3) previous myocardial infarction,[5] (4) hyperventilation,[6] (5) effects of various drugs such as digitalis and quinidine,[7] (6) ST-T wave abnormalities at rest,[8] (7) electrolyte imbalance,[9] (8) carbohydrate loading,[10] (9) psychotropic drugs,[11] and (10) preexcitation syndromes. Because of these limitations, exercise with thallium-201 (Tl-201) myocardial perfusion imaging and radionuclide blood pool imaging has become increasingly important for the diagnosis of and evaluation of coronary artery disease.

Exercise Myocardial Thallium Imaging

Background

Before 1973, several gamma-emitting radionuclides had been used to assess regional myocardial perfusion at rest in patients with suspected coronary artery disease. These agents included radioisotopes of potassium (K-42, K-43) and its analog (cesium-129).[12,13] These agents were efficiently extracted from the blood by the sodium-potassium adenosine triphosphatase system. Although these agents were useful in detecting infarction, it was not until 1973 that Zaret et al.[14] reported the administration of potassium-43 at peak exercise to detect exercise-induced perfusion defects in 28 of 34 patients with coronary artery disease. No defects were seen in 12 of 12 patients without coronary artery disease. This group of investigators[15] also demonstrated that exercise imaging

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with potassium-43 was normal in patients with normal coronary arteries and positive electrocardiographic exercise tests. Subsequently the use of rubidium-81 for myocardial imaging was described[16] as well as its increased diagnostic accuracy in detecting coronary artery disease during exercise imaging compared with electrocardiographic exercise testing alone.[17]

Kawana et al.[18] suggested the use of thallium-199 as a perfusion imaging agent on the basis of biologic similarities between thallium and potassium. Subsequently Tl-201 was used to obtain myocardial scintiscans in the goat[19] and this demonstrated peak myocardial concentration at 10 to 25 minutes after injection. Tl-201 has the advantages of lower photon energies and greater myocardial concentration (1.7 to 3.7 percent of the administered dose) compared with potassium-43, rubidium-81 and cesium-129.[20,21] The suitability of Tl-201 for imaging with the unmodified gamma scintillation camera and its longer half-life make it more practical for clinical use. In 1976 early reports[22,23] appeared describing the use of Tl-201 imaging with exercise as a noninvasive test for detecting coronary artery disease.

Exercise Imaging Procedure

Thallium redistribution: Early experiences with exercise myocardial Tl-201 imaging utilized separate injections of the radionuclide during exercise and at rest. Tl-201 was injected at peak exercise; the patient was then imaged at the termination of exercise. If these initial images were abnormal demonstrating a defect, the patient returned at least 72 hours later and was reinjected with Tl-201 and reimaged. If the Tl-201 defect persisted on repeat images, then myocardial scar was said to be present. If the Tl-201 perfusion defect was no longer present on repeat images, then transient exercise-induced myocardial ischemia was said to be present during exercise. In 1976, our laboratory[24] reported the disappearance of Tl-201 myocardial defects present on initial images in experimental dogs over a 2 hour period after transient ischemia. This phenomenon was referred to as Tl-201 redistribution. Tl-201 redistribution on serial images after a single dose of Tl-201 given at peak exercise was subsequently observed in patients with coronary artery disease.[24] When this technique was used, defects observed on images immediately after exercise that filled in on the delayed images were believed to represent ischemia, whereas initial defects that persisted were believed to represent scarring. We have found in the animal laboratory as well as clinically that most redistribution occurs within 3 to 4 hours. Berman et al.[25] have observed continued Tl-201 redistribution for up to 24 hours. However, we believe that if some redistribution has not occurred by 3 to 6 hours, the myocardium is probably irreversibly damaged. Furthermore, although biologic elimination of Tl-201 is minimal (10 percent excreted in 10 days) and physical decay of Tl-201 is about 22 percent of the dose in 24 hours, images taken 24 hours after the Tl-201 dose are usually technically inadequate. Blood et al.[26] demonstrated a comparable diagnostic accuracy for coronary artery disease in the exercise Tl-201 test when redistribution images were substituted for images at rest.

Single dose Tl-201 exercise testing with redistribution images offers the additional advantages of (1) a lower radiation dose to the patient, (2) requiring only one patient visit, (3) one half the cost for radiopharmaceutical, and (4) reduction in background activity compared with images obtained after Tl-201 is injected at rest. Finally, our laboratory and others have reported transient Tl-201 myocardial defects on initial images at rest in some patients with severe coronary artery stenosis, which compromises myocardial blood flow at rest.[27,28] Initial defects on Tl-201 images at rest can therefore represent either scar or ischemia. Use of the delayed imaging approach to distinguish between scar and ischemia eliminates this possible source of confusion. A recent review[29] describes the theoretic and practical considerations of the Tl-201 redistribution phenomenon.

Stress testing: The level of stress, rather than the method used to produce the stress, appears to be most important in determining the sensitivity of the Tl-201 exercise test for coronary artery disease. We have found no difference in the sensitivity of the Tl-201 exercise test using upright treadmill exercise (87 percent) in 161 patients with coronary artery disease or supine bicycle exercise (86 percent) in 50 patients with coronary artery disease. Handgrip was reported[30] to produce adequate stress for diagnostic evaluation using Tl-201 myocardial imaging, although we would not recommend this approach in patients capable of dynamic exercise. Although pacing-induced stress has been suggested by some groups, a recent report[31] has questioned the adequacy of heart rate stress alone for Tl-201 studies.

In our laboratory patients are generally exercised in an upright position on a treadmill. A 12 lead electrocardiogram is obtained and an intravenous line is inserted before exercise. Patients are then exercised using a standard graded exercise protocol. Electrocardiographic leads are recorded at 3 minute intervals and selected leads are monitored continuously. Patients are exercised until there is symptom limitation by either chest pain, shortness of breath or fatigue, unless a bothersome arrhythmia or substantial S-T segment depression occurs at which time exercise is terminated. Approximately 45 seconds before the termination of exercise, 1.5 mCi of Tl-201 is injected intravenously. Immediately after the completion of exercise (initial images) and 3 to 6 hours later (delayed images), imaging is performed with the patient supine in the anterior and 50° and 70° left anterior oblique projections. Images are obtained with an Anger scintillation camera interfaced to an imaging computer system. A medium sensitivity collimator and a 20 to 30 percent energy window encompassing the 68 to 80 keV X-ray emissions of Tl-201 are used. When the gamma camera permits the use of multiple photopeaks, both the X-ray and gamma ray photopeaks (135 and 167 keV) can be used to increase photon yield.[20] When a dose of 1.5 mCi of Tl-201 is used, adequate numbers of photons can be collected within 5 to 10 minutes. We routinely collect all images for a preset time of between 6 and 10 minutes. The use of fixed imaging intervals may allow one to quantitate changes in Tl-201 activity over serial images. A minimum of 300,000 counts should be collected in the initial image. Although we do not recommend Tl-201 imaging without a computer, if imaging is performed using an isolated gamma camera, images should be collected for a preset number of counts to allow for direct comparison of serial images.

Interpretation of Thallium-201 Exercise Studies

Interpretation is generally qualitative although quantitative approaches have been suggested. In our laboratory qualitative interpretation is carried out as follows: Tl-201 images are viewed directly on a computer screen with initial and delayed images displayed side by side for comparison in each projection. The left ventricular activity is divided into anterolateral, apical and inferior segments on the anterior view, and septal, apical-inferior and posterior segments on the left anterior

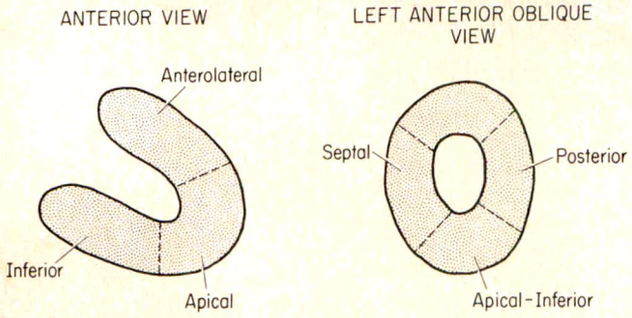


FIGURE 1. Division of left ventricular myocardium into segments for assessment of thallium-201 myocardial images. Activity is not assessed in the superior segment in the left anterior oblique projection because activity is normally reduced or absent in this area.

oblique view (Fig. 1). Each segment is subjectively scored using a simple grading system: zero (minimal activity), 0.5, 1.0, 1.5 and 2.0 (normal activity). A transient defect is defined as an increase of one or more grades from initial to delayed image for any ventricular segment. A transient defect is interpreted as representing transient ischemia occurring during exercise. A persistent defect for the anterolateral, inferior, septal or posterior segments is defined as an exercise and delayed grade of 1.0 or less. The apical and apical-inferior segments can have reduced activity under normal circumstances because of the myocardium being thinner in these segments. Thus, a significant persistent defect for the apical and apical-inferior segments is defined as an exercise and delayed grade of 0.5 or less. A persistent defect is interpreted as representing myocardial scar. Defects that fulfill the criteria for both a transient and a persistent defect (partial redistribution) are believed to represent ischemia plus scar or severe ischemia. Figure 2 demonstrates the clinical patterns found on exercise-delayed Tl-201 imaging studies: normal, transient defect and persistent defect. Cook et al.[32] have described the appearance of the normal Tl-201 myocardial image in detail.

In addition to the uniformity of Tl-201 activity in the myocardium over time, images are also subjectively evaluated for (1) size of ventricular cavity, (2) thickness of ventricular walls, and (3) pulmonary Tl-201 activity relative to myocardial activity. When evaluating myocardial Tl-201 distribution in images where the ventricular cavity clearly changes in size between initial and delayed images, it is important to remember that decreases or increases in left ventricular wall thickness can lead to the appearance or disappearance of defects on images without an actual change in tracer distribution.[33]

Clinical Experience With Exercise Thallium Imaging

Sensitivity of thallium-201 imaging: Table I summarizes most of the reported experience with exercise myocardial Tl-201 imaging for the detection of coronary artery disease. Sensitivity is defined as patients with true positive results divided by all patients with coronary artery disease, and specificity as patients with true negative results divided by all patients without coronary artery disease. Some studies employed the two dose, exercise-rest Tl-201 technique and others used the single dose Tl-201 approach. However, because Blood et al.[26] demonstrated that both techniques differentiate between ischemia and scar, and because sensitivity and

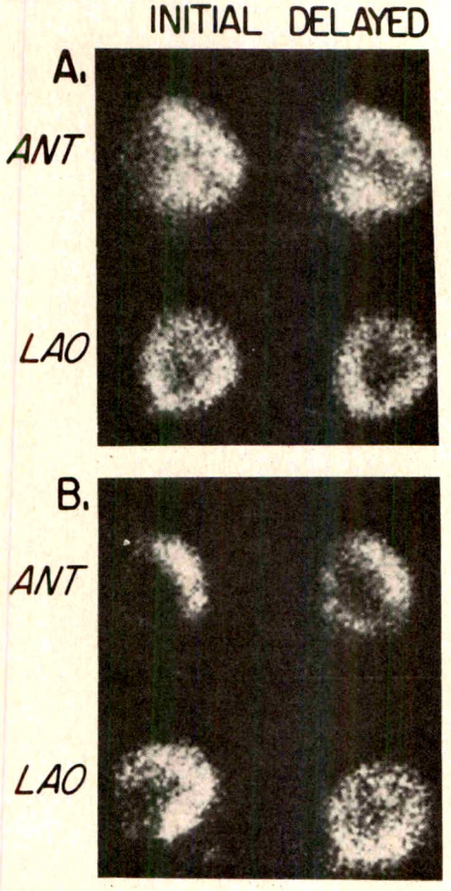


FIGURE 2. A, normal thallium-201 myocardial images immediately after exercise (INITIAL) and 4 hours later (DELAYED). Note the homogeneous distribution of tracer except for the apical and apical-inferior segments, where activity can normally be slightly lower. **B,** abnormal thallium-201 myocardial images. Note the inferior and apical defects in the initial anterior (ANT) view, and septal and apical-inferior defects in the initial left anterior oblique view (LAO). There is complete redistribution into the septal and apical-inferior segments (transient defect), partial redistribution into the inferior segment, and no redistribution into the apical defect (persistent defect).

specificity are related only to initial images after exercise (that is, the appearance of an initial defect), the results are combined in Table I. In 1,817 patients, the overall sensitivity and specificity of the Tl-201 exercise test for coronary artery disease were 82 and 91 percent, respectively. When studies from Table I that did not report exercise electrocardiographic data were excluded, the Tl-201 exercise test had a sensitivity of 82 percent and a specificity of 90 percent. The overall sensitivity and specificity of the electrocardiographic exercise test for coronary artery disease were 60 and 81 percent, respectively. In most studies, diagnostic Q waves on the electrocardiogram at rest were considered a sufficient criterion for coronary artery disease. Using chi square analysis, the Tl-201 exercise test was significantly more sensitive ($p < 0.0001$) and specific ($p < 0.05$) for coronary artery disease than the electrocardiographic exercise test.

The improved sensitivity of Tl-201 exercise imaging

TABLE I

Reported Results of Thallium-201 Exercise Test

Year	Principal Investigator (location)	Patients (n)	Tl-201		ECG	
			Sens	Spec	Sens	Spec
1976	Klein (London, Ontario)[121]	144	59/73	69/71	61/73	63/71
1976	Peterson (San Diego)[122]	25	16/17	4/8	12/17	5/8
1977	Bailey (Baltimore)[35]	83	46/63	20/20	26/63	20/20
1977	Ritchie (Seattle)[123]	101	58/76	23/25	50/76	21/25
1977	Lenaers (Belgium)[124]	70	52/55	14/15	—	—
1977	Rosenblatt (San Francisco)[125]	18	14/15	3/3	6/8 (7 ND)	2/2 (1 ND)
1978	Carrillo (Detroit)[126]	55	34/39	16/16	21/39	12/16
1978	Verani (Iowa City)[127]	82	38/48	33/34	42/48	21/34
1978	Turner (Chicago)[128]	64	23/34	29/30	25/34	23/30
1978	Ritchie (Multiple Centers)[129]	190	115/148	37/42	62/148	37/42
1978	Bodenheimer (Philadelphia)[130]	45	21/32	13/13	15/32*	—
1978	Johnstone (New Haven)[131]	33	18/26	7/7	—	—
1979	McCarthy (New York)[38]	128	81/95	26/33	61/95	30/33
1979	Pohost (Boston)[40]	209	140/161	36/48	103/161	37/48
1979	Dash (San Francisco)[42]	96	66/81	15/15	30/81	12/15
1979	Verani (Houston)[132]	58	38/46	12/12	30/46*	—
1979	Vogel (Denver)[72]	65	31/42	22/23	—	—
1979	Meller (New York)[133]	55	23/28	23/27	—	14/24 (3 ND)
1979	Okada (Boston)[34]	49	27/33 (6 ND)	9/10 (1 ND)	23/27 (11 ND)	3/4 (7 ND)
1979	Hecht (Los Angeles)[134]	56	46/46	8/10	32/46	7/10
1979	Caldwell (Seattle)[135]	39	30/33	6/6	—	—
1979	Borer (Bethesda)[136]	53	35/43	9/10	—	—
1979	Verani (Houston)[137]	38	17/21	17/17	—	—
1979	Kirshenbaum (Boston)[138]	61	43/50	10/11	32/50	11/11
Total		1,817	1,071/1,305 0.82	461/506 0.91	631/1,044 0.60	318/393 0.81

* Does not include Q waves at rest.

ECG = exercise electrocardiogram; ND = nondiagnostic or technically inadequate studies; Sens = sensitivity = true positive results ÷ all patients with disease; Spec = specificity = true negative results ÷ all patients without disease; — = data not reported.

over electrocardiographic exercise testing is due, in part, to the larger number of patients with nondiagnostic or inconclusive electrocardiographic exercise tests due to either baseline electrocardiographic changes or inability to achieve 85 percent predicted maximal heart rate.[34–38] The accuracy of the Tl-201 exercise test, although also dependent on the level of exercise achieved,[39] does not appear to be as critically related to this factor as the electrocardiographic exercise test. In a series of 227 patients admitted to our institution for coronary angiography, there was no significant difference in sensitivity for those patients who achieved 85 percent predicted maximal heart rate and those patients who did not.[40] The Tl-201 exercise study has been found particularly useful in patients with equivocal electrocardiographic tests because of hyperventilation, drug effect, ventricular hypertrophy, intraventricular conduction delay and bundle branch block, preexcitation syndrome or previous myocardial infarction.[37,41] The sensitivity of the Tl-201 exercise test for coronary artery disease increases with the increasing extent of diseased vessels and increasing severity of stenosis.[42–44] The sensitivity is also high for left main coronary artery disease, but the specificity is low.[42,45] Sensitivity decreases in the presence of coronary collateral vessels[46] and in patients taking propranolol with a negative electrocardiographic exercise test.[40]

Specificity of thallium-201 imaging: The improved specificity of the Tl-201 exercise test over the electrocardiographic test in coronary artery disease is due, in part, to the many causes for false positive electrocardiographic exercise tests, some of which were mentioned previously. We[47] demonstrated the Tl-201 exercise test was quite specific in patients without a history of typical anginal chest pain and with a positive electrocardiographic exercise test (91 percent). Other investigators[48,49] also used the Tl-201 exercise test in asymptomatic patients with a positive electrocardiographic exercise test to predict the presence or absence of coronary artery disease. We[50] demonstrated that the specificity of the Tl-201 exercise test is quite low when patients with isolated subcritical stenosis (30 to 45 percent diameter narrowing) are included in the control group. Fifty percent of these patients have positive Tl-201 exercise images in a distribution appropriate for the involved coronary artery. Although these subcritical lesions have conventionally been assumed to have little clinical importance, it may be inappropriate to consider these positive Tl-201 exercise images as false positive results, because inequalities in coronary perfusion were described in association with such lesions using xenon-133 washout techniques.[51–53] Furthermore, the length and number of "subcritical" lesions can contribute to their significance. We must also admit that the reliability of the coronary arteriogram in differentiating truly subcritical (less than 50 percent lesions)

from critical lesions is probably not great, because the angiographic projection and the significance of a lesion at rest may change with stress. The interobserver agreement on the significance of lesions in this borderline range is small. Because of the uncertainty in interpreting the degree of coronary arterial narrowing angiographically, the Tl-201 stress test may indeed be a means of clarifying the hemodynamic significance of a coronary lesion. At present the diagnostic accuracy of any of these radionuclide approaches can be enhanced with patient selection. For example, the use of young asymptomatic volunteers as a control group might lead to a high specificity because the incidence of even subcritical disease is small and their ability to exercise large. Further, because sensitivity is related to the extent of disease, a group with a large incidence of three vessel disease would show a higher sensitivity than one with single vessel disease.

Other causes of positive test: The specificity of the Tl-201 exercise test for coronary artery disease has been determined in most studies using patients presenting with chest pain who have required and undergone coronary angiography. It is possible that other disease processes may cause altered myocardial perfusion and could explain some apparent false positive results in this group. Preliminary results from one group[54] have demonstrated a large incidence of abnormal right ventricular myocardial biopsies in patients with positive Tl-201 exercise tests and normal coronary arteries. If changes in cellular integrity as well as decreases in flow can lead to decreased Tl-201 uptake, then this increased prevalence of ultrastructural abnormalities may explain some false positive results. Positive results in patients with aortic stenosis and normal coronary arteries may be due to exercise-induced subendocardial ischemia[55] or exercise-induced changes in left ventricular wall thickness.[33] Positive results have been reported in patients with coronary arterial anomalies[56] and in some patients with myocardial bridges.[57,58] There is debate regarding idiopathic hypertrophic subaortic stenosis and the presence[59,60] or absence[61] of positive Tl-201 exercise test results. Although false positive results have been reported in association with mitral valve prolapse, most reports have not substantiated this observation.[62–64]

In a series of 227 patients, we have not found the overall specificity of the Tl-201 exercise test to be significantly different in men versus women, in patients who achieved 85 percent or greater predicted maximal heart rate versus those who did not, and in patients taking propranolol versus those who were not.[40] However, in patients with negative electrocardiographic exercise tests, a significantly reduced specificity occurred in women (56 percent) compared with men (81 percent), and in patients taking propranolol (53 percent) compared with those who were not (82 percent). Lack of specificity in women may have been due in part to attenuation of myocardial activity by overlying breast.

Correlation with left ventricular functional state: Tl-201 exercise testing produces functional information as well as diagnostic information. Total,

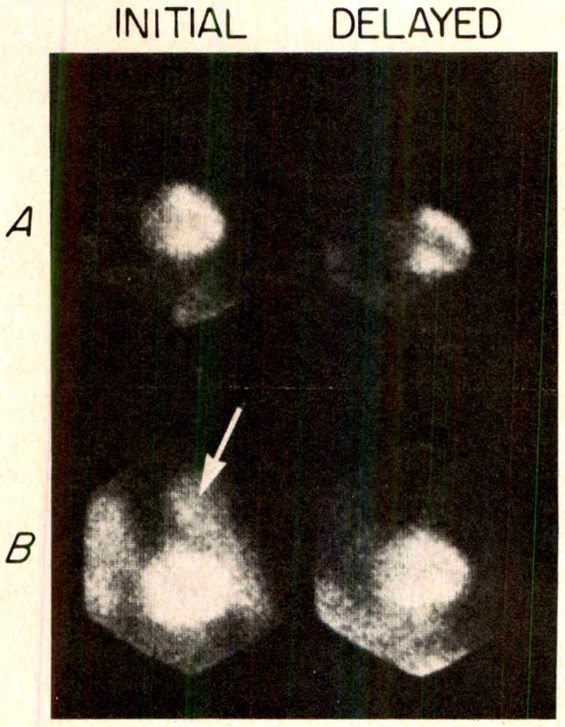


FIGURE 3. Thallium lung activity. **A,** normal exercise thallium-201 study with minimal lung uptake of the tracer. **B,** exercise thallium-201 study showing increased thallium-201 lung activity initially after exercise (**arrow**) but only minimal lung activity in the delayed images.

partial or no redistribution into a defect on initial Tl-201 images is associated with increasing frequency and severity of wall motion abnormalities.[65] Asynergic segments at rest with redistribution on serial postexercise Tl-201 imaging demonstrate reversibility during ventriculography after a premature ventricular contraction.[66,67] Asynergic segments at rest with persistent defects on serial Tl-201 exercise imaging demonstrate irreversible asynergy on ventriculography after a ventricular premature contraction. Finally, in an additional series of 61 patients in our laboratory[68] we have correlated the presence of transient or persistent Tl-201 defects to exercise-induced changes in global left ventricular function assessed by multigated cardiac blood pool imaging. In the presence of redistribution, the ejection fraction decreased with exercise whereas in the presence of a persistent defect, ejection fraction showed a flat response with no significant change during exercise. Finally, in the group of patients in whom the Tl-201 images were normal, the ejection fraction increased significantly with exercise. These observations are consistent with the hypothesis that a transient Tl-201 defect represents transient ischemia leading to a deterioration of ejection fraction with exercise. A persistent defect represents scar which causes a blunting of the normal increase in ejection fraction with exercise. Apparently normal regional flow distribution even in the presence of coronary artery disease of angiographic significance appears to be associated with preservation of a normal global response to exercise.

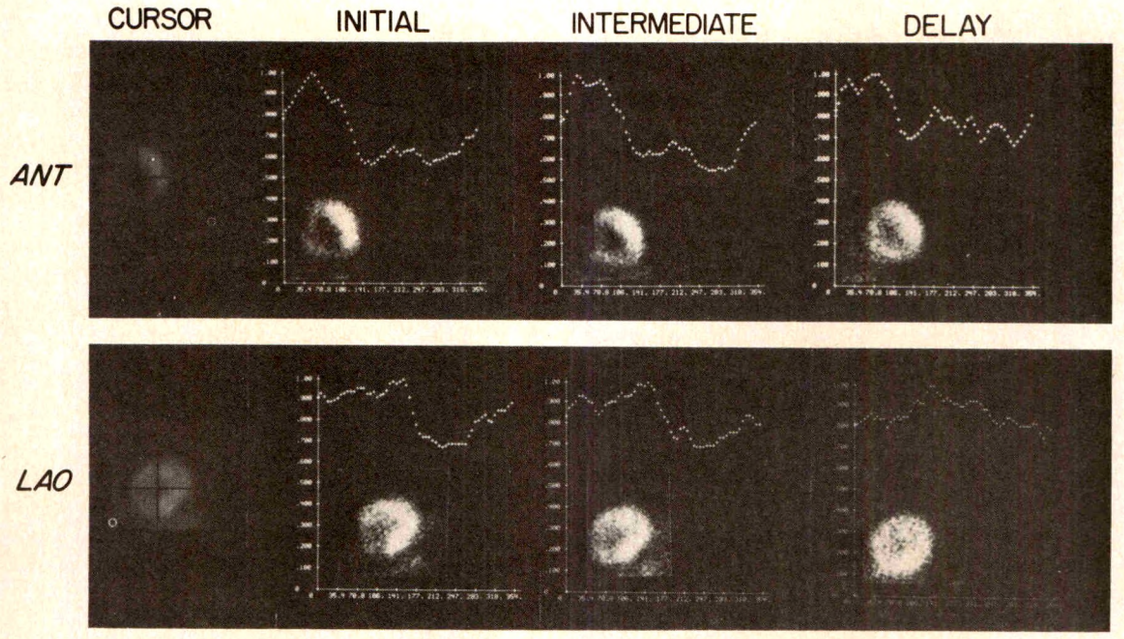


FIGURE 4. Quantitation of myocardial thallium-201 distribution. The left column demonstrates the position of the cursors, which have been set by the operator at the center of the ventricular cavity. Starting at 12 o'clock and proceeding clockwise, the program constructs radial lines from the center to the periphery and plots the maximal picture element counts on the X-Y graph. This figure demonstrates quantitation of the transient and persistent defects observed in the same patient presented in Figure 2B. ANT = anterior; LAO = left anterior oblique.

Other Considerations

Increased Tl-201 lung activity: Such increased activity has been observed on initial Tl-201 exercise images in certain patients (Fig. 3). We have attempted to determine its clinical significance by quantitating this Tl-201 lung activity in 39 patients with coronary artery disease and 10 normal subjects.[69] Computer-determined Tl-201 lung activity was expressed as a percent of maximal myocardial Tl-201 activity for initial Tl-201 images. The mean lung/heart Tl-201 ratio was 37.6 ± 2.5 percent (standard error of the mean) for normal patients, 45.5 ± 3.6 percent for patients with single vessel coronary disease, and 53.5 ± 2.1 percent for patients with multivessel disease. When a lung/heart ratio more than 2 standard deviations above the normal mean was defined as abnormal, all patients with exercise-induced perfusion defects and an abnormal lung/heart ratio had coronary artery disease. Thus, the specificity of this combination of findings on Tl-201 exercise images is very positive for coronary artery disease. An increased Tl-201 lung/heart ratio was found to correlate with an exercise-induced increase in simultaneously measured pulmonary capillary wedge pressure in seven patients.[70] Five additional patients had no increase in wedge pressure and a normal Tl-201 lung/heart ratio. The increase in pulmonary capillary wedge pressure with the resultant increase in pulmonary blood volume may lead to an increase in capillary volume and thus capillary surface area. The increase in surface area may result in a larger net extraction of Tl-201 during its passage through the pulmonary circulation.

Observer variance: The interobserver variance in the subjective scoring of segmental Tl-201 activity has been determined in our laboratory using four independent observers.[71] When segmental Tl-201 scores were interpreted by an individual observer using a standard method using one set of criteria applied to all ventricular segments, the sensitivity was 77 percent and specificity 75 percent for coronary artery disease. When segmental Tl-201 scores were interpreted using a set of criteria derived from the analysis of variance and individualized for each ventricular segment, the sensitivity and specificity increased to 85 percent ($p < 0.05$) and 78 percent (p = not significant), respectively. The diagnostic accuracy of the Tl-201 exercise test is significantly improved by accounting for the interobserver variance in the interpretation of images. Quantitation of Tl-201 activity on images also holds promise for reducing the error due to observer variance. Figure 4 demonstrates one approach for the quantitation of myocardial Tl-201 activity. Several groups of investigators are currently using similar approaches to quantitation for the interpretation of Tl-201 exercise tests.[72–74] Quantitative approaches to the interpretation of Tl-201 exercise test have been shown to be both sensitive and specific for coronary artery disease and may be of particular value in situations in which observers are inexperienced.

Tomographic imaging: Tomographic approaches to Tl-201 myocardial imaging have been reported to improve the diagnostic accuracy of the Tl-201 exercise test. Vogel et al.[72] demonstrated a higher sensitivity without loss of specificity using the Tl-201 exercise test with tomographic imaging compared with planar imaging.

Imaging during coronary vasodilation: Albro and

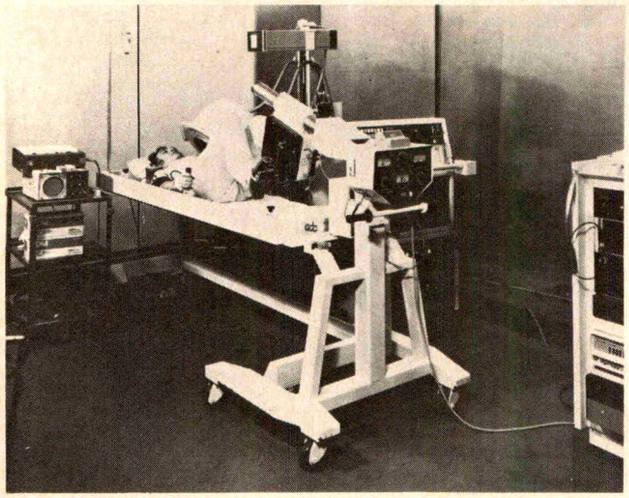


FIGURE 5. Supine bicycle ergometer equipment for performing exercise radionuclide angiography.

Gould and co-workers[75,76] have described myocardial imaging of Tl-201 injected at rest and during coronary vasodilatation induced with intravenously administered dipyridamole. The technique is based on the fact that significant coronary stenoses that do not compromise blood flow at rest will compromise the hyperemic response of blood flow during coronary vasodilatation. This group of investigators found images obtained after administration of dipyridamole to be equal to or better in quality than those obtained after exercise. The diagnostic accuracy for coronary artery disease was the same for Tl-201 imaging after administration of dipyridamole and Tl-201 exercise imaging. Francisco et al.[74] also demonstrated a high accuracy using the dipyridamole approach combined with tomographic imaging using a tomographic collimator. This technique may reduce some of the risks inherent in exercise and may be particularly well suited to patients whose exercise capability is limited.

Exercise Radionuclide Angiography

Background

In 1969 Mason et al.[77] measured ventricular function by the bolus injection of a radiopharmaceutical and the rapid sequential visualization of the heart using a scintillation camera (first pass method). In the same year, Mullins et al.[78] used an R wave triggered signal to obtain an end-diastolic blood pool image of the heart after the direct injection of tracer into the left ventricle. In 1971, Strauss and Zaret and co-workers[79,80] used electrocardiographic gating to obtain end-diastolic and end-systolic equilibrium blood pool images of the heart, thus making calculation of ejection fraction and evaluation of regional wall motion possible. Since that time, advances in computer technology and intrinsic gamma camera resolution have allowed acquisition at multiple points in the cardiac cycle, with real time cine display of the equilibrium blood pool data.[81,82] In 1976 Borer et al.[83] described the use of supine exercise equilibrium radionuclide angiography for the detection of coronary artery disease. They demonstrated that patients with coronary artery disease are unable to increase their ejection fraction with maximal exercise and also exhibit new regional wall motion abnormalities with exercise.

Exercise Imaging Procedure

In our laboratory, patients are studied using the equilibrium blood pool technique. A description of the first pass technique can be found in the review by Ashburn et al.[84] Patients are given 3 mg of stannous pyrophosphate intravenously, followed 30 minutes later by 20 mCi of technetium-99m pertechnetate to complete the in vivo red blood cell label. Patients are then imaged at rest in the anterior projection, and then in the left anterior oblique projection which displays the interventricular septum with uniform thickness from top to bottom to maximize separation between right and left ventricular blood pools (approximately 45° to 50° left anterior oblique). We use a high resolution parallel hole collimator and a conventional Anger scintillation camera with the pulse height analyzer set at 140 keV with a 20 percent window. Multigated acquisitions are collected using a commercially available imaging computer system and an electrocardiographic physiologic synchronizer. After imaging at rest patients are exercised in the supine position on a table with an attached bicycle ergometer, shoulder restraints and hand grips to minimize patient motion during exercise (Fig. 5). Exercise is initiated at a work load of 150 kilopond meters/minute and is increased by 150 kilopond meters/minute every 3 minutes. Electrocardiographic leads are recorded at 3 minute intervals before increasing the work load. Selected leads are monitored continuously. Multigated equilibrium blood pool imaging is performed during the final 2 minutes of each exercise period. Patients are exercised until symptoms, hypotension, arrhythmia or marked ST segment changes occur.

Many factors in this outlined protocol are varied in different laboratories including (1) type of gamma camera (single versus multicrystal), (2) type of approach (first pass versus gated equilibrium), (3) radiopharmaceutical, (4) exercise position and equipment, and (5) exercise protocol. Many of these variables have been discussed[4]; some of them may have an effect on the accuracy of the approach. For example, the superior accuracy reported by Borer et al.[83] may in part be related to the use of list mode acquisition used by that group compared with gated acquisition used by our group. List mode acquisition collects all data as they occur along with the electrocardiogram. Gating is performed later on selected cycles with nearly uniform cycle lengths. Gated acquisition divides up the cardiac cycle before computer storage and variable cycle lengths may be superimposed. This superimposition may lead to reduced resolution and reliability of ejection fraction measurements especially with exercise when heart rate may be changing from initiation of image collection until its termination. However, gated acquisition permits sequential evaluation of left ventricular function and wall motion not possible with the first pass technique.

Interpretation of Exercise Radionuclide Angiographic Studies

In our laboratory, blood pool images at rest and exercise are displayed side by side as endless loop movies. Wall motion is assessed qualitatively as follows: The ventricle is divided into anterolateral, apical and inferior walls on the anterior view, and septal, apicoinferior and posterior walls on the left anterior oblique view (Fig. 6). Regional wall motion is scored using a 5 point scale: three = normal, two = mild hypokinesia, one

= moderate to severe hypokinesia, zero = akinesia, and −one ≙ dyskinesia. Half points in the grading system are used when an observer feels that the motion of a segment is intermediate between two grades. A decrease of one or more grades in regional wall motion score with exercise for any segment or a regional wall motion score of less than 1.5 for any segment at rest is considered evidence of coronary artery disease (Fig. 7).

Rest and exercise multigated blood pool image ejection fractions are calculated using a computer program with a variable region of interest. A box is positioned to encompass the left ventricle in the left anterior oblique end-diastolic frame. Beginning at the center, the program searches outward radially until a matrix point is less than a threshold percent of the peak left ventricular value. This threshold can be altered by the observer. In this manner the left ventricular edge is defined for each frame of the study. The program then calculates ejection fraction based on counts within the varying regions of interest minus background counts. However, many of the commercially available automatic edge detection systems occasionally fail to recognize the left ventricular-left atrial border. Therefore, close supervision by the operator is required to generate an accurate ejection fraction. Failure of the ejection fraction to increase by at least 5 percent during exercise is considered evidence of coronary artery disease (Fig. 7 and 8). Slutsky et al.[85] demonstrated that the normal increase in ejection fraction with exercise is due primarily to a decrease in end-systolic volume, whereas the exercise-induced decrease in ejection fraction in patients with angina is due primarily to an increase in end-systolic volume. Patients with coronary artery disease who do not exhibit angina have no change in ejection fraction with exercise because there is no significant change in end-systolic volume.

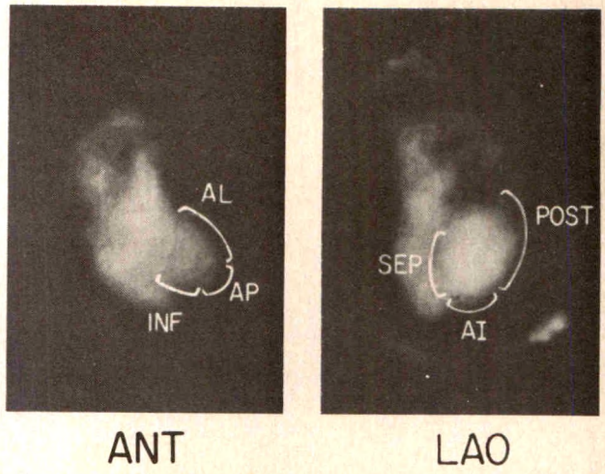


FIGURE 6. Segmented division of left ventricular blood pool for regional wall motion assessment. AI = apical-inferior segment; AL = anterolateral segment; ANT = anterior view; AP = apical segment; INF = inferior segment; LAO = left anterior oblique view; POST = posterior segment; SEP = septal segment.

Clinical Experiences With Exercise Radionuclide Angiography

Sensitivity and specificity: Table II summarizes the reported experience with exercise radionuclide angiography for the detection of coronary artery disease in 427 patients. A new regional wall motion abnormality induced by exercise had a sensitivity of 73 percent and a specificity of 100 percent for coronary artery disease. Failure to increase the left ventricular ejection fraction with exercise had a sensitivity of 87 percent and a specificity of 93 percent for coronary artery disease. When a new regional wall motion abnormality or a failure to increase ejection fraction was used as sufficient criterion for disease, exercise radionuclide angiography had an overall sensitivity of 87 percent and a specificity of 92 percent. When studies from Table II

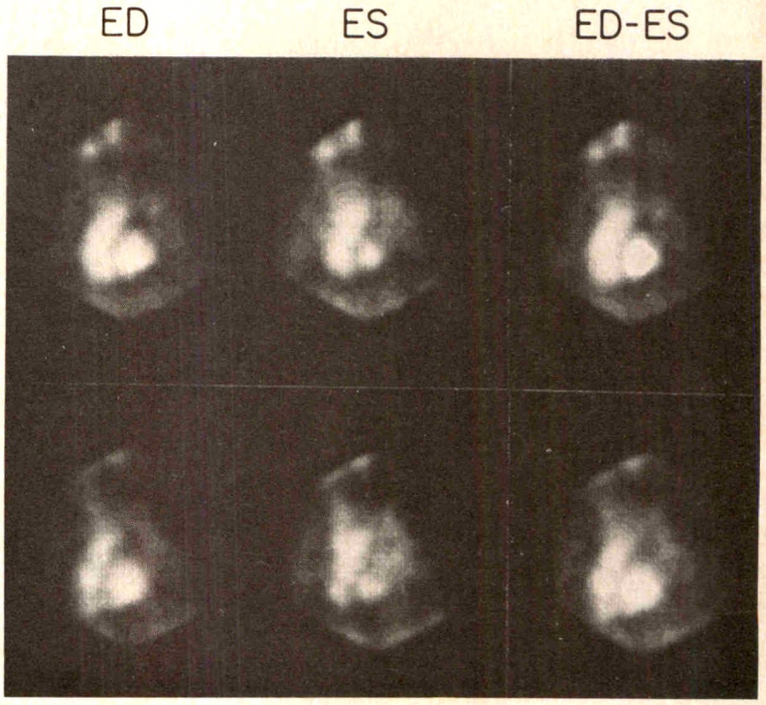


FIGURE 7. Exercise radionuclide angiography study demonstrating normal ejection fraction (EF) response to exercise. ED = end-diastolic frame; ED-ES = end-diastolic frame with superimposition of end-systolic left ventricular blood pool outline; ES = end-systolic frame.

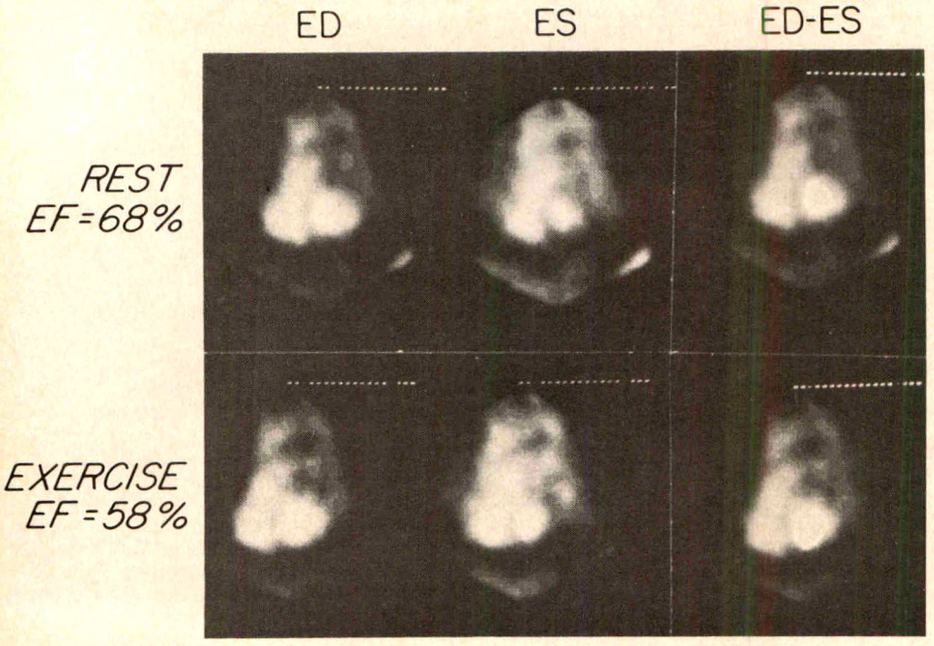


FIGURE 8. Exercise radionuclide angiography study demonstrating abnormal ejection fraction (EF) response to exercise. Abbreviations as in Figure 7.

that did not report exercise electrocardiographic data were excluded, exercise radionuclide angiography had a sensitivity of 90 percent and a specificity of 90 percent. The electrocardiographic exercise test had a sensitivity of 64 percent and a specificity of 98 percent. Exercise radionuclide angiography was significantly more sensitive ($p < 0.0001$) than the exercise electrocardiographic test when analyzed by chi squared analysis. The specificity of the exercise electrocardiogram was not significantly higher at 98 percent than that of exercise radionuclide angiography at 90 percent.

The higher sensitivity of exercise radionuclide angiography compared with electrocardiographic exercise testing is most likely due to the fact that electrical changes occur at a higher ischemic threshold than contractile changes. Scheuer and Brachfeld[86] have shown that contractile changes do precede electrical changes in the ischemic myocardium. Using serial exercise radionuclide imaging, Upton et al.[87] have demonstrated that ejection fraction changes precede electrocardiographic changes in patients with coronary artery disease.[83]

TABLE II

Reported Results of Blood Pool Angiographic Exercise Test

Year	Principal Investigator (location)	Method	Patients (n)	RWM		EF		RWM + EF		Ex ECG	
				Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec
1978	Rerych (Durham)[95]	Erect first pass	60	24/30	—	29/30	27/30	29/30	27/30	23/30	—
1979	Borer (Bethesda)[139]	Supine gated	84	59/63	21/21	56/63	21/21	60/63	21/21	43/63	20/21
1979	Berger (New Haven)[90]	Supine or erect first pass	73	28/60	13/13	44/60	13/13	52*/60	13/13	33/60	13/13
1979	Jengo (Torrance)[140]	Erect first pass	19	11/11	8/8	11/11	8/8	11/11	8/8	7/11	—
1979	Caldwell (Seattle)[135]	Supine + erect gated	39	—	—	31/33	4/6	—	—	—	—
1979	Borer (Bethesda)[136]	Supine gated	53	—	—	—	—	40/43	10/10	—	—
1979	Verani (Houston)[137]	Supine gated	38	—	—	—	—	11/21	16/17	—	—
1980	Kirshenbaum (Boston)[138]	Supine gated	61	—	—	—	—	38/50	6/11	32/50	11/11
Total			427	122/164 0.73	42/42 1.00	171/197 0.87	73/78 0.93	241/276 0.87	101/110 0.92	138/214 0.64	44/45 0.98

* Includes four patients with abnormalities at rest only.

EF = failure to increase ejection fraction by 5 percent with exercise; Ex ECG = abnormal exercise electrocardiogram; RWM = exercise-induced regional wall motion abnormality; Sens = sensitivity; Spec = specificity; — = data not reported.

Factors influencing sensitivity of radionuclide angiography: The effects of propranolol on the diagnostic accuracy of exercise radionuclide angiography for coronary artery disease have been debated. Although several investigators[88–90] demonstrated no difference in diagnostic accuracy in patients receiving or not receiving propranolol, other investigators[91,92] reported a propranolol-induced amelioration of exercise-induced left ventricular dysfunction in patients with coronary artery disease. Such an effect would tend to reduce the sensitivity of the test for coronary disease. The specificity of exercise radionuclide angiography for coronary artery disease may also be reduced in patients taking propranolol.[92,93] This effect appears to be due to a reduction in heart work at peak stress, because no blunting of the normal ejection fraction response to exercise was found when patients reached comparable heart rates with and without propranolol.[94]

Factors that increase the sensitivity of exercise radionuclide angiography for coronary disease include (1) increasing levels of stress,[90] (2) the presence of electrocardiographic evidence of ischemia,[90] (3) left main coronary arterial stenosis,[95] and an increased number of diseased vessels.[96] Factors that may decrease the sensitivity of the test include (1) treatment with nitrates,[97] (2) depressed ejection fraction at rest,[98] and (3) coronary arterial collateralization.[99] Nitroglycerine may also decrease the sensitivity of exercise radionuclide angiography for coronary artery disease.[100]

Other factors inducing abnormal response to exercise: While discussing specificity, it is important to remember that exercise radionuclide angiography is not specific for coronary artery disease. An abnormal ejection fraction response to exercise would be expected in any condition in which there is reduced left ventricular reserve such as volume or pressure overload states and states of decreased left ventricular compliance, as well as ischemic states. Abnormal ejection fraction responses to exercise have been reported in patients with aortic stenosis,[101] aortic regurgitation,[102] mitral regurgitation,[103] mitral valve prolapse,[104] idiopathic hypertrophic subaortic stenosis,[105] chronic obstructive pulmonary disease,[106] beta thalassemia and chronic iron overload[107] and cystic fibrosis.[108]

Only studies using dynamic exercise stress were included in Table II. Other studies have used other forms of stress such as pacing, cold[109] and isometric handgrip.[30] A decreased sensitivity for coronary artery disease using isometric handgrip stress compared with dynamic exercise was found in one study[110] but not in a second study.[111] Isometric handgrip stress and first pass radionuclide angiography were found to have a sensitivity of 86 percent and a specificity of 87 percent for coronary artery disease.[112]

Interobserver variance: We[113] have recently reported the interobserver variance in determining an exercise-induced change in regional wall motion by radionuclide angiography. Only exercise-induced changes in ejection fraction that exceed the values for interobserver variance can be considered significant (Fig. 9). With regard to the left anterior oblique segments that

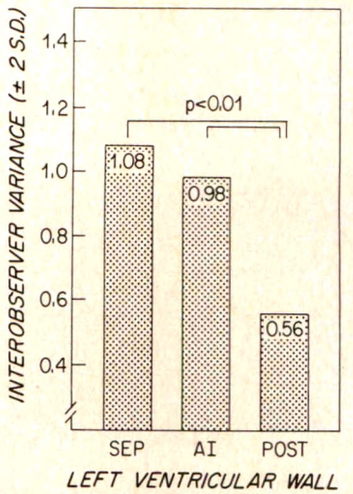


FIGURE 9. Interobserver variance for an exercise-induced change in regional wall motion as assessed by radionuclide angiography, expressed as ±2 standard deviations (S.D.) (five point scoring system). Left ventricular walls are septal (SEP), apical-inferior (AI) and posterior (POST). (Reprinted from Okada et al.[113] by permission of the American Heart Association, Inc.)

are visualized during exercise, interobserver variance was significantly increased for the septal and apical-inferior segments compared with the posterior segment ($p < 0.01$). We[113] have also reported the interobserver variance (two standard deviations = 11.4 percent) and the intraobserver variance (two standard deviations = 11.0 percent) in the quantitation of an exercise-induced change in ejection fraction. We found that the observer variance can be significantly reduced (two standard deviations = 4.6 percent) ($p < 0.05$) by comparing averaged ejection fractions derived from at least two separate determinations for both the rest and the exercise radionuclide angiograms. Interpretation based on criteria derived from observer variance analysis should improve the specificity of the exercise radionuclide test for coronary artery disease. We recommend that each institution determine this variance for best diagnostic reliability.

Other Considerations

Pulmonary volume ratio: We have recently reported[89] that the sensitivity of exercise radionuclide angiography can be significantly improved without changing the specificity by determining the ratio of pulmonary blood pool activity (pulmonary blood volume) at rest compared with that during exercise. The pulmonary blood volume ratio was determined by placing a computer-generated region of interest over the left lung in the rest and exercise left anterior oblique end-diastolic frames (Fig. 10). The pulmonary blood volume ratio was determined by dividing the counts obtained during exercise by the counts obtained at rest corrected for differences in acquisition times for the two studies. Exercise radionuclide angiography had a sensitivity for coronary artery disease of 64 percent before

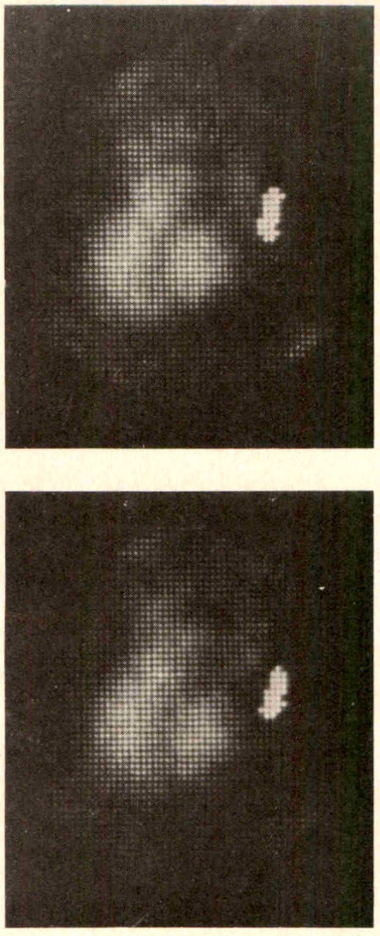


FIGURE 10. End-diastolic frames for radionuclide angiograms in the left anterior oblique projection at rest (**top**) and during exercise (**bottom**). The regions of interest for the determination of the pulmonary blood volume ratio are included. The ratio of pulmonary blood volume during exercise compared with that at rest was 1.16 in this patient with coronary artery disease. (Reprinted from Okada et al.[89] by permission of *The New England Journal of Medicine*.)

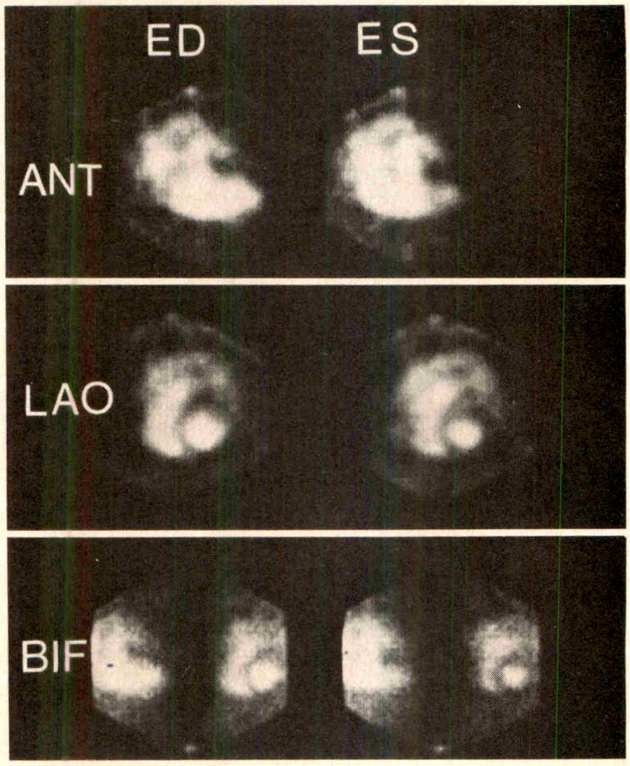


FIGURE 11. Gated blood pool images obtained in the same patient with (1) a single plane collimator in the anterior (ANT) and left anterior oblique projections (LAO), and (2) a bifocal (BIF) collimator. ED = end-diastolic; ES = end-systolic. (Reprinted from Boucher et al.[114] by permission of the *Journal of Nuclear Medicine*.)

the additional criterion of a pulmonary blood volume ratio of 1.06 or more, and 90 percent when this criterion was included ($p < 0.005$). There was no change in specificity using this ratio. Also, the ratio was insensitive for isolated proximal right coronary arterial stenosis, possibly because of protection of pulmonary blood volume by right ventricular dysfunction or because left ventricular involvement was less in such patients.

Current developments: Two developments in instrumentation may ultimately improve the diagnostic accuracy of exercise radionuclide angiography. A bifocal diverging collimator has been developed that allows simultaneous biplane imaging of the heart during equilibrium radionuclide angiography (Fig. 11).[114] Good correlation was noted between biplane and single plane determined regional wall motion and ejection fraction. Imaging in two planes during exercise may allow detection of regional wall motion abnormalities present in the anterior projection. The second advance in instrumentation is the development of tomographic techniques for blood pool imaging.[115,116] Tomography during exercise may detect localized areas of asynergy not apparent on planar imaging.

Exercise Myocardial Thallium Imaging Versus Exercise Radionuclide Angiography

This review discusses two approaches to the diagnostic evaluation of patients with coronary artery disease. The Tl-201 approach relies on detection of inhomogeneities in radionuclide uptake by the myocardium due to relatively reduced perfusion or inability of scar to concentrate the agent. Exercise radionuclide angiography relies on detection of a deterioration in regional function or an absence of an appropriate increase in ejection fraction during exercise.

Comparative Sensitivity and Specificity

Table III summarizes the results of studies that have compared the diagnostic accuracies of exercise Tl-201 myocardial imaging and exercise radionuclide angiography in 315 patients evaluated for coronary artery disease. The Tl-201 exercise test had a sensitivity of 82 percent and a specificity of 95 percent for coronary artery disease. The exercise radionuclide angiogram had a sensitivity of 82 percent and a specificity of 84 percent. Although the sensitivities for the two techniques were

TABLE III

Reported Results of Thallium-201 Versus Blood Pool Exercise Test

Year	Principal Investigator (location)	Patients (n)	Tl-201		Blood Pool	
			Sens	Spec	Sens	Spec
1978	Johnstone (New Haven)[131]	33	18/26	7/7	20/26	7/7
1979	Caldwell (Seattle)[135]	39	30/33	6/6	31/33	4/6
1979	Borer (Bethesda)[136]	53	35/43	9/10	40/43	10/10
1979	Massie (San Francisco)[141]	16	8/10	6/6	10/10	6/6
1979	Verani (Houston)[137]	38	17/21	17/17	11/21	16/17
1979	Kirshenbaum (Boston)[138]	61	43/50	10/11	38/50	6/11
1979	Bodenheimer (Philadelphia)[30]	75	46/56	17/19	46/56*	15/19*
Totals		315	197/239	72/76	196/239	64/76
			0.82	0.95	0.82	0.84

* Handgrip exercise.
Blood Pool = exercise radionuclide angiography; Sens = sensitivity; Spec = specificity.

identical, the specificity of the exercise radionuclide angiogram was significantly lower than that of the exercise Tl-201 image ($p < 0.05$ by chi squared analysis). The lower specificity of the exercise radionuclide angiogram can be explained by the large number of conditions listed previously that can cause an abnormal ejection fraction response to exercise other than ischemia. These conditions include volume overload, pressure overload and restrictive and congestive states. In contrast, transient and localized persistent defects on exercise Tl-201 images are comparatively specific for an ischemic condition.

Although Table III includes one study that utilized isometric handgrip stress, the results were not significantly different when this study was excluded. The Tl-201 exercise test had a sensitivity of 83 percent and a specificity of 96 percent. The exercise radionuclide angiogram had a sensitivity of 82 percent and a specificity of 86 percent.

Rationale for the Combined Use of Exercise Thallium-201 Imaging and Exercise Radionuclide Angiography

The pathogenesis of ischemic heart disease and its consequences should be reviewed briefly. First, when disease is minimal, its only clinical evidence might be small insignificant plaques demonstrable only by coronary angiography. Under these circumstances flow can increase during maximal demand without impediment. As the disease progresses and plaques enlarge, a point is reached where the ability of a given artery to accommodate an increase in flow during a maximal stress becomes mildly to moderately limited. In other words, flow through nondiseased or less diseased arterial segments increases appropriately for the demand whereas flow through the segment under discussion is somewhat less. If our ability to detect perfusion inhomogeneities were exquisitely sensitive, the perfusion imaging approach would provide the earliest means of detecting coronary artery disease. The fact that many patients with subcritical stenosis angiographically have a positive Tl-201 exercise test lends support to the sensitivity of the perfusion scanning approach for detecting early disease.[50]

As the disease progresses, further limitation of flow with increased demand will lead to an end organ response to this perfusion versus demand imbalance. The most sensitive indicator of this imbalance is reduction in mechanical function of the myocardium. Some investigators[117] have suggested that it is diastolic function that deteriorates before systolic function. A study[89] showing a rise in pulmonary blood volume with exercise as being a more sensitive indicator of ischemia than change in ejection fraction supports this premise to some extent. The increase in pulmonary blood volume without a decrease in ejection fraction suggests earlier deterioration of diastolic left ventricular function. Of course systolic function also is sensitive to reduction in perfusion.[118] Even small reductions in flow can lead to subtle decreases in regional left ventricular function as sensitively measured by sonomicrometer crystals.

Nuclear imaging versus electrocardiogram: Advanced disease leads to ischemic electrocardiographic changes and finally angina pectoris with maximally increased demand. The lower sensitivity of the electrocardiogram and angina pectoris as compared with either Tl-201 or radionuclide angiographic approaches is consistent with these observations. Scheuer and Brachfeld[86] found that contractile changes do precede electrical changes in the ischemic myocardium, providing further rationale for the increased sensitivity of functional changes over electrocardiographic changes in the clinical setting.

Thus, both exercise Tl-201 imaging and exercise radionuclide angiography should be more sensitive for coronary artery disease than the exercise electrocardiogram. Exercise Tl-201 imaging that detects the perfusion imbalance which initiates functional ischemia should, in theory, be a more sensitive approach for detecting coronary artery disease than exercise radionuclide angiography, which detects functional alterations resulting from ischemia. In addition, the use of dipyridamole and Tl-201 provides an approach to detection of disease without necessarily inducing functional ischemia. However, because both the detection of perfusion abnormalities and the assessment of their functional consequences are important, access to both of these exercise radionuclide techniques is most desirable.

TABLE IV

Relative Strengths and Weaknesses of Exercise Tl-201 Imaging and Exercise Radionuclide Angiography

Exercise Tl-201 Imaging	Exercise Radionuclide Angiography
Strengths	Weaknesses
1. No definite need for computer	1. Definite need for computer
2. Detects ischemia which may precede wall motion abnormality	2. Detects abnormal left ventricular systolic function which occurs after ischemia has occurred
3. Can be performed in conjunction with routine treadmill exercise electrocardiogram	3. Need special supine exercise table with bicycle ergometer and gating device
4. May be more specific for coronary artery disease	4. May be less specific for coronary artery disease
Weaknesses	Strengths
1. Tl-201 must be acquired commercially within several days of scheduled test	1. Technetium is generator-produced and readily available
2. Tl-201 is expensive compared with technetium	2. Technetium is inexpensive compared with Tl-201
3. Expertise is needed for qualitative interpretation	3. Ejection fraction calculation is semiautomated
4. Functional consequences of perfusion abnormality unknown	4. Detects functional consequences of ischemia

Recommendations for the Combined Use of Exercise Thallium-201 Imaging and Exercise Radionuclide Angiography

Factors determining which diagnostic procedure to do first: Although Table III demonstrates a higher specificity for coronary artery disease when exercise Tl-201 imaging is performed compared with the results of exercise radionuclide angiography, the number of control patients is small. Thus, in deciding which of these two approaches to perform first to detect coronary disease one must consider other factors in addition to relative diagnostic accuracies. Many of these factors are listed in Table IV, which compares the strengths and weaknesses of the two radionuclide techniques: (1) Considerable experience is necessary for accurate qualitative interpretation of exercise Tl-201 images and regional wall motion on gated blood pool studies. Exercise radionuclide angiography requires less experience because the ejection fraction determinations are semiautomated. (2) An exercise treadmill is available in most institutions, whereas a supine exercise table and bicycle ergometer are not as commonly available. (3) Relative costs for performing the two exercise radionuclide procedures may differ between institutions. The cost of the Tl-201 test is higher than that of technetium-99m, although the cost of processing the data is higher using the gated or first pass angiographic studies. (4) Tl-201 has a relatively short half-life and must be acquired within several days before the exercise test. The temporal availability of Tl-201 may differ depending on the geographic location of the institution.

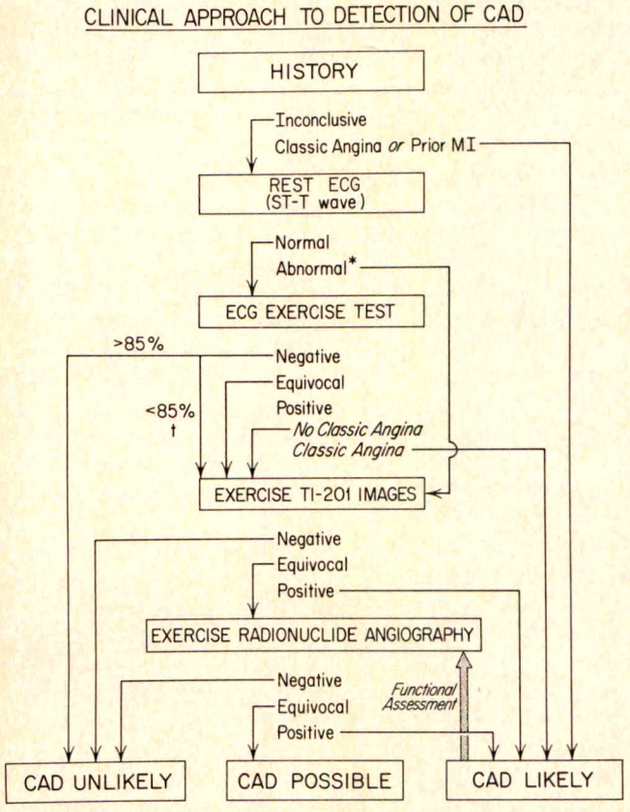


FIGURE 12. Flow chart describing a clinical approach to the detection of coronary artery disease (CAD). See text for discussion. ECG = electrocardiogram; MI = myocardial infarction; Tl-201 = thallium-201.

* Includes pathologic Q waves in electrocardiogram at rest.

† If the patient fails to achieve 85 percent or greater predicted maximal heart rate and if the electrocardiographic response to exercise is negative, then exercise Tl-201 imaging is performed.

Recommended protocol: Figure 12 presents the scheme used frequently at our institution for the noninvasive evaluation of the patient presenting with chest pain. The presence of typical angina by itself is quite specific for coronary artery disease. We use the Tl-201 exercise test diagnostically before exercise radionuclide angiography because of its lower cost and higher specificity for coronary artery disease at our institution. If the diagnosis is still unclear after the Tl-201 exercise test, or if the diagnosis of coronary artery disease is clear but functional information is desired, then exercise radionuclide angiography is performed. Exercise radionuclide angiography may also have value in assessing the effects of coronary bypass graft surgery[119] and in evaluating patients after myocardial infarction.[120]

We currently recommend that exercise Tl-201 imaging be performed in patients whose resting electrocardiogram is abnormal, or whose electrocardiographic exercise test is either (1) equivocal, (2) positive without classic angina pectoris, (3) positive in a young

woman or (4) negative with an inadequate heart rate response to exercise. In these patients we recommend discontinuing propranolol if possible before proceeding with exercise Tl-201 imaging.

Summary

Both exercise Tl-201 imaging and exercise radionuclide angiography improve the sensitivity and specificity for coronary artery disease over that of electrocardiographic exercise testing alone. Both techniques also offer information regarding the functional consequences of coronary artery disease. Access to both approaches is most desirable because each has an important role in the evaluation of patients with possible coronary artery disease.

Acknowledgment

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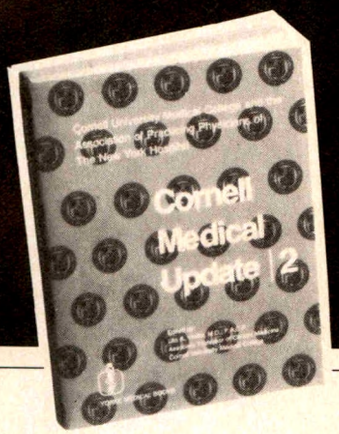
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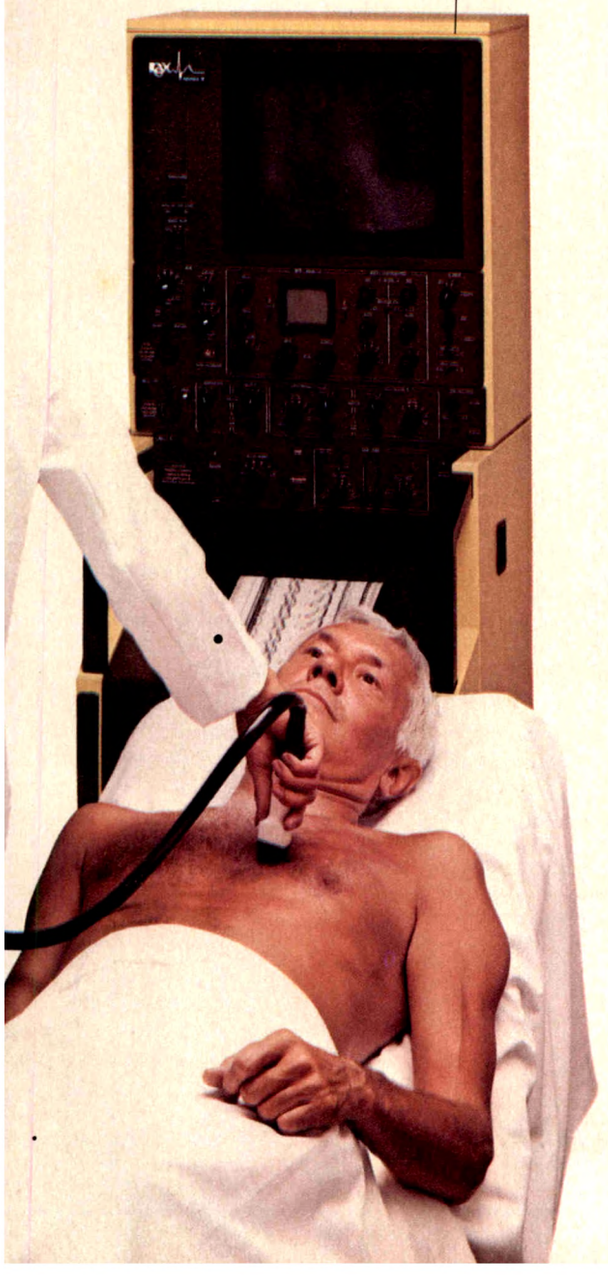
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Echocardiography in Acute and Remote Myocardial Infarction

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Two dimensional echocardiography is just beginning to be used to characterize cardiac damage in patients with acute myocardial infarction. The two dimensional approach allows for a more comprehensive evaluation of cardiac anatomy and is able to detect with high sensitivity changes in regional wall motion that previously were sometimes missed or only found with difficulty using M mode echocardiography. Two dimensional echocardiography appears to offer a basis for quantifying the extent of myocardial damage in acute myocardial infarction and thus may permit objective assessment of therapeutic modalities and prognosis. In addition, the technique facilitates recognition of specific complications in acute myocardial infarction. In particular, the technique offers the ability to distinguish true from false ventricular aneurysm, postinfarction ventricular septal defect from papillary muscle dysfunction and rupture, and right ventricular infarction from cardiac tamponade.

By its nature clinical coronary artery disease is a process that impairs coronary blood flow in one or more segments of the coronary arterial tree. When coronary flow is reduced to a point inadequate to meet the demands of metabolism in a given area of the heart, tissue ischemia leads to regional myocardial dysfunction. Experimental and clinical characterization of the regional myocardial dysfunction, which occurs in coronary artery disease, has been the subject of continued investigation over the past half century. This review will outline some of the experimental background pertaining to regional myocardial dysfunction in coronary artery disease and will describe in detail observations made during the past decade using both M mode and two dimensional echocardiography in patients with acute and remote myocardial infarction.

Observations in Experimental Animals

Over the past five decades a number of acute animal experiments using differing techniques have shown abnormalities of regional contraction to occur in the distribution of an acutely ligated coronary artery shortly after its occlusion. Most frequently cited are the original studies of Tennant and Wiggers[1] in which epicardial myographic recordings showed within seconds after coronary occlusion new systolic aneurysmal bulging of the acutely ischemic distal area.

M mode echocardiography in experimental coronary occlusion: During the past 10 years, ultrasonic methods have been used to study the effects of acute and sustained ischemia further. Appreciation of regional contraction abnormalities *within,* rather than on the surface of the heart has been possible by implanting ultrasonic sonomicrometers in pairs in control subendocardial regions preserved from and in test areas subjected to experimental ischemia.[2] Conventional single crystal M mode echocardiograms have also been used to study endocardial motion during induced acute ischemia either by placing the transducer on the wall of the closed chest dog or more commonly on the surface of

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TABLE I
Regional Wall Motion Abnormalities Detected in Experimental Animals With Ultrasonic Techniques

Ischemic or Injured Area
Abnormal bulging during isovolumic systole
Decreased amplitude of motion during systolic ejection
Decreased velocity of motion during systolic ejection
Impaired systolic wall thickening
Normally Perfused Area
Compensatory hyperactivity in healthy remote areas
Transitional wall motion abnormalities in adjacent areas

the heart of the open chest dog. By passing the ultrasonic beam through the interventricular septum and left ventricular posterior wall, the behavior of opposite sides of the heart can be observed when one or the other wall is made ischemic.[3,4]

Abnormalities of contraction as seen in the transmyocardial view rendered by M mode echocardiography are also apparent within seconds after experimental coronary occlusion. During isovolumic systole there is aneurysmal bulging of the ischemic segment away from the center of the left ventricular cavity; during the ejection phase of systole the amplitude and velocity of motion of the ischemic wall are reduced compared with control values; the wall fails to thicken and may even be observed to become thinner. Regions adjacent to the ischemic area can show transitional forms of motion abnormalities between normal and ischemic regions. Often remote regions, particularly the opposite wall, will show compensatory hyperactivity; that is, the septum will show increased velocity and amplitude of motion when the posterior wall is ischemic and the posterior wall will show similar changes when the septum is ischemic. The abnormalities of left ventricular wall motion commonly detected with echocardiography in acute animal experiments are recapitulated in Table I.

Two dimensional echocardiography in acute myocardial infarction: This method is beginning to be used to observe the effects of acute myocardial infarction in closed chest dogs. The two dimensional technique enables the investigator to examine the extent of abnormal wall motion associated with acute coronary occlusion; in one recent study the amount of wall motion abnormality correlated with infarct size determined with technetium pyrophosphate scintigraphy.[5] Wall motion abnormalities have also been positively correlated with peak rise in serum creatine kinase values.[6]

Attention is also being paid to analysis of changes in A mode echocardiographic signals backscattered from the acutely ischemic myocardium. Acute ischemia and injury increase the amplitude and change the frequency distribution of backscattered signals; computer-aided signal analysis can distinguish such evidence of injury from normal myocardium.[7,8] Using two dimensional echocardiography, Kisslo et al.[9] reported a qualitatively echo-dense "speckle" pattern appearing in acutely infarcted canine myocardial walls. These hard echoes appear in the first few days of infarction and perhaps represent an evolution of the increased amplitude A mode signals seen shortly after acute coronary ligation.

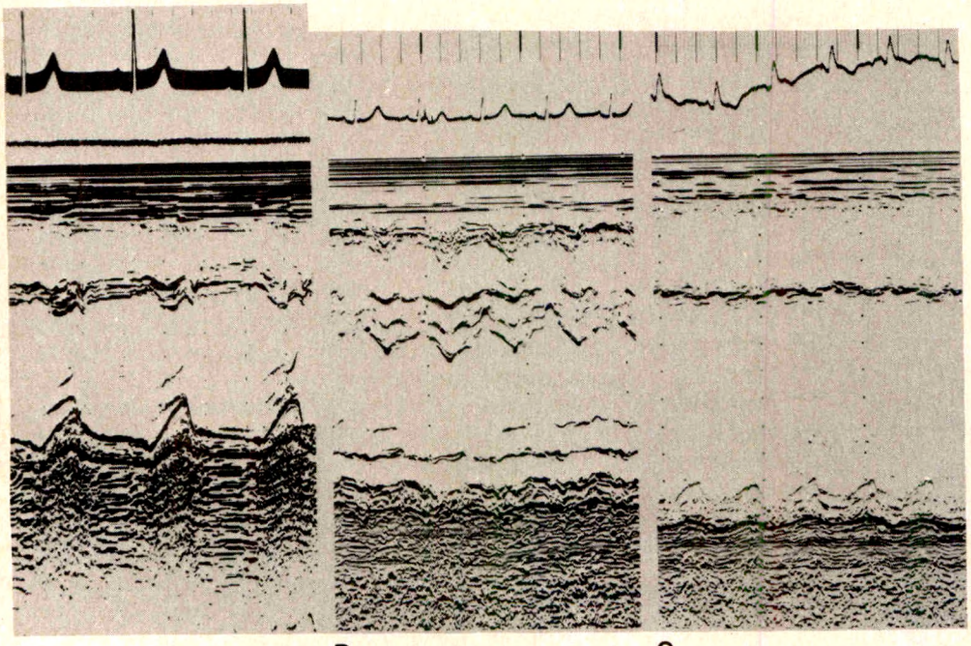


FIGURE 1. M mode echocardiograms from normal patient (**A**), patient with acute inferoposterior myocardial infarction (**B**) and patient with remote anteroseptal myocardial infarction (**C**). The amplitude of left ventricular posterior wall motion and its systolic thickening are diminished in the patient with acute infarction (**B**). Also, there is hyperactivity of the interventricular septum which can be conceptualized as compensating for the poor posterior wall motion. In the patient with remote anterior infarction (**C**) the same features affecting the interventricular septum are evident. In addition, the septum is relatively echo-dense compared with the posterior wall and is thin in diastole (approximately 6 mm).

Clinical Observations

M Mode Echocardiography

One of the earlier observations made with M mode echocardiography in a patient with acute myocardial ischemia is directly analogous to the results of the animal experiments cited. These occurred in a patient with Prinzmetal's angina who had angiographically documented coronary arterial spasm but no fixed obstructions in the distribution of the left anterior descending coronary artery.[10] This patient had a striking loss of the amplitude of systolic septal motion during ischemic episodes characterized by chest pain and associated with S-T segment elevation and T wave peaking in mid precordial electrocardiographic leads. The amplitude of septal motion returned to normal as the clinical episodes abated and electrocardiographic manifestations of the ischemic process resolved. This observation underscores the appropriateness of the animal models discussed because comparable regional myocardial dysfunction is seen with clinical episodes of ischemic pain and the changes appear immediately with evidence of onset of the ischemic process.

Abnormal left ventricular wall motion: Several systematic studies performed in patients admitted to coronary care units with the diagnosis of acute myocardial infarction have further confirmed the observation that impaired amplitude of wall motion is a finding highly associated with regional myocardial damage. A typical example is shown in Figure 1. In a series of 64 patients with acute transmural myocardial infarction, Corya et al.[11] reported abnormal left ventricular wall motion in the echocardiogram corresponding to the electrocardiographic site of infarction in 84 percent of the group. Thirty percent of these patients had exaggerated motion in noninfarcted areas, an observation consistent with the compensatory hyperactivity noted in the animal experiments cited. Table II summarizes the echocardiographic measurements of the amplitude of motion compared with the normal range in those patients in the series of Corya et al.[11] with well localized anterior and inferior myocardial infarction.

Detection of wall motion abnormalities with M mode echocardiography is critically dependent on traversing the abnormally contracting myocardial segment with the echographic beam. Because some myocardial infarcts are not necessarily in the path of the standard M mode study, further techniques have been developed with this study and successfully used particularly to detect abnormal anterior wall motion in patients with anterior infarction. These techniques usually involve further lateral exploration of the left precordium at multiple sites in a search for a "window" through which the anterior left ventricular wall can be directly imaged. When this approach[12] is used, absent or paradoxical anterior left ventricular wall motion is a frequent finding in patients with anterior infarction, whereas anterior wall motion abnormalities are rarely seen in patients with inferior infarction.

Dynamic changes in wall thickness: Because abnormalities of wall motion, particularly of the interventricular septum, are nonspecific findings and occur in patients with other conditions, notably right ventricular volume overload and chronic cardiomyopathy, closer scrutiny has been devoted to other local properties of the myocardium in the affected region in patients with acute infarction. In this regard, dynamic changes in wall thickness in transition from diastole to systole have received a great deal of attention as a manifestation of impaired regional function in contraction caused by myocardial ischemia. In a series of 40 patients with acute myocardial infarction (composed of equal numbers with anterior and inferior infarcts),[13] 18 of the 20 with an anterior infarct had abnormally decreased septal systolic thickening, 19 had abnormally decreased septal motion and 18 had both decreased septal thickening and abnormal wall motion. Interestingly, 11 of these patients had systolic septal *thinning*. Of the 20 patients with inferior infarction, 65 percent had abnormally decreased posterior wall thickening, 18 abnormally decreased posterior wall motion and 13 both the thickening and motion abnormalities. Systolic thinning of the posterior wall was infrequently recorded, being seen in only one patient. Abnormalities of wall motion and systolic thickening can be seen, although less frequently, in patients with chronic coronary artery disease, particularly if there has been an antecedent myocardial infarction. However, systolic thinning is highly suggestive of acute injury since it is an unusual finding outside of the setting of acute myocardial infarction.

Changes in myocardial scarring: Further observations have resulted in the emergence of criteria that identify myocardial scar tissue as a residual of previous myocardial infarction. In a series of 182 patients Rasmussen et al.[14] showed that scar tissue was very likely to be present if (1) the myocardium was less than 7 mm thick in diastole and more echo-producing than the adjacent or opposing wall, or (2) an area of myocardium was 30 percent less thick than an adjacent area in the same scan (Fig. 1C). These observations were confirmed in all instances by surgical observations and in 34 cases by histologic examination of either autopsy or surgical

TABLE II
Wall Motion Amplitude in Normal Subjects and Patients With Acute Myocardial Infarction*

	Normal	Site of Infarction	
		Anterior	Inferior
Septal amplitude			
Range (cm)	0.3–0.8	0–0.6	0–2.0
Mean	0.63	0.08	0.81
% decreased	—	80%	3%
% increased	—	0%	39%
Posterior wall amplitude			
Range (cm)	0.8–1.6	0.8–2.1	0–1.7
Mean	1.29	1.40	0.66
% decreased	—	0%	57%
% increased	—	16%	7%

* Adapted from Corya et al.[11]

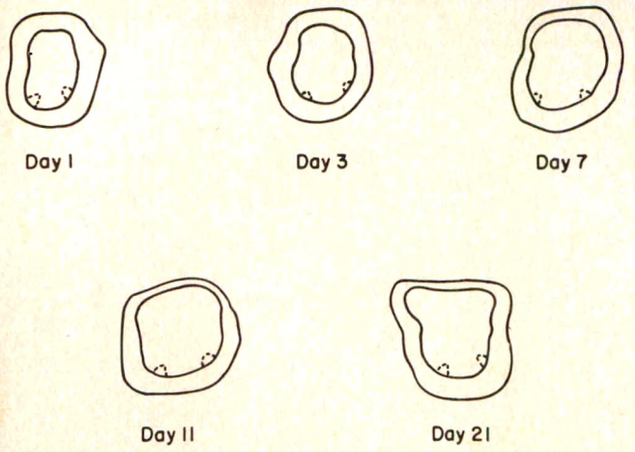


FIGURE 2. Epicardial and endocardial diastolic outlines of short axis views of the left ventricle at the level of the papillary muscles in a patient with an acute transmural anterior infarction and evidence of infarct expansion over the course of serial studies. The development of regional dilatation and thinning in the infarcted areas is apparent from the tracing of day 7. (Reprinted by permission, from Eaton et al.[17])

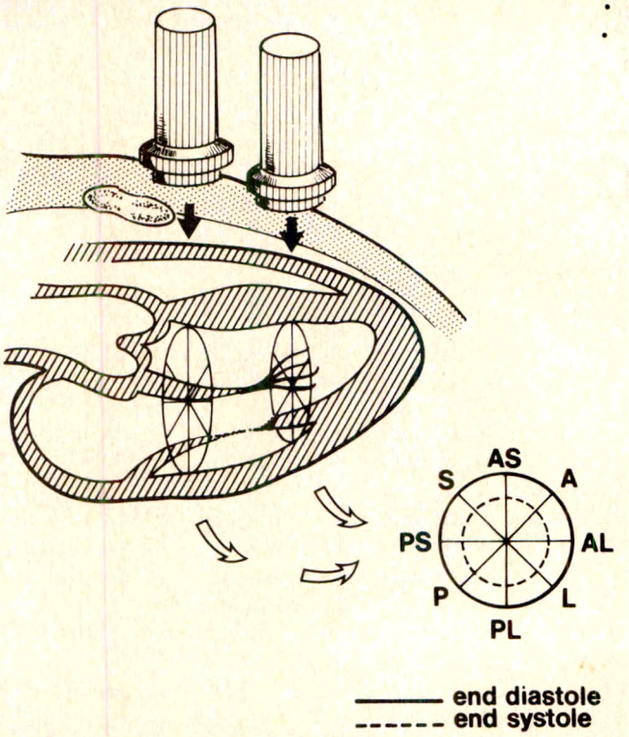


FIGURE 3. Schematic drawing illustrating short axis views of the left ventricle obtained with two dimensional echocardiography. The insert shows diastolic and systolic outlines of the left ventricle at either level as a pair of outlines that approximate concentric circles. The axis system used for analysis is superimposed. Regional function of the left ventricle can be characterized with use of either segmental areas or chords (see text). A = anterior; AL = anterolateral; AS = anteroseptal; L = lateral; P = posterior; PL = posterolateral; PS = posteroseptal; S = septal.

resection specimens. Ninety percent of these patients had a clinical history of antecedent myocardial infarction and most had consistent electrocardiographic findings as well.

Two Dimensional Echocardiography

Acute myocardial infarction: Two dimensional echocardiography offers the ability to evaluate regional abnormalities of myocardial motion with much greater facility than M mode examination since the field of the examination is not restricted to the narrow M mode beam and the spatial orientation of the tomographic sections can be appreciated. As early as 1977 Kisslo et al.[15] reported that two dimensional echocardiograms lent themselves as readily to qualitative examination of regional wall motion abnormalities as did left ventricular cineangiograms. More recently several observers have looked specifically at two dimensional echocardiography for its ability to detect wall motion abnormalities that are associated with acute myocardial infarction. Most observers have depended on one or more short axis views that allow evaluation of departures from the normally concentric contraction of the left ventricle around its perimeter. Heger et al.[16] devised a nine segment subdivision of the left ventricle that included anterior, medial, posterior and lateral quadrants at the mitral and papillary muscle levels and an apical segment recorded by placing the transducer directly over the apex and obtaining a long axis scan. Complete studies, allowing evaluation of these nine segments, was accomplished in 37 of 44 attempts. Nineteen of 20 patients with inferior infarction had asynergy in posterior segments, 14 patients with anterior infarction had asynergy in anterior segments and 3 patients with both anterior and inferior infarction had appropriately localized wall motion abnormalities. In four patients pathologic localization of infarction corresponded to the asynergic areas detected on two dimensional echocardiography, thus confirming that this technique is a reliable method of detecting and localizing regional contraction abnormalities that occur in acute myocardial infarction.

Eaton et al.[17] performed *serial* two dimensional echocardiographic examinations in 28 patients during the first 2 weeks after myocardial infarction. Diastolic short axis two dimensional echocardiograms at the level of the papillary muscle tips were evaluated serially in this study in patients whose first echocardiogram had been obtained within 60 hours of the acute event. Endocardial and epicardial outlines were traced; segment lengths and wall thickness were calculated using a computer-aided semiautomated contouring system. Eight of the patients showed evidence of *infarct expansion* with disproportionate transmural thinning of the infarcted zone and associated left ventricular dilatation, whereas the remaining 20 patients had no evidence of these findings. Patients with anterior and anteroseptal infarction seemed particularly prone to infarct expansion (Fig. 2). At 8 weeks after infarction 4 of the 8 patients who showed infarct expansion had died, whereas all 20 patients without infarct expansion were

living. On the basis of this study these investigators contended that infarct expansion, rather than further extension of the ischemic process with further necrosis of myocardial tissue, might play a more important role than had previously been appreciated in patients surviving acute myocardial infarction. This study demonstrates that two dimensional echocardiography can be used as an indicator of topographic changes that occur in the evolution of an acute myocardial infarction and may have considerable clinical importance, not only in assessing survival but potentially in assessing interventions that may influence survival of such patients.

Remote myocardial infarction: Using a computer-aided approach in our laboratory, we[18,19] have also been interested with the ability of two-dimensional echocardiography to define and quantify regional wall motion abnormalities. We obtained cross-sectional short axis views of the left ventricle in a series of normal volunteers, patients with coronary artery disease without remote myocardial infarction as well as patients with a prior myocardial infarction confirmed by abnormal Q waves in the electrocardiogram. End-diastolic short axis outlines of the ventricle at both mitral valve and papillary muscle levels were traced with a light pen digitizing system using the onset of the electrocardiographic QRS complex as a marker of end-diastole. Similarly, end-systolic frames were traced using the first high frequency component of the second heart sound as an indicator of end systole. At each tomographic level the mid point of the interventricular septum on the left ventricular endocardial surface was identified by the observer. From this starting point an initial axis (Fig. 3, axis SL) was constructed using a computer algorithm to that point on the lateral left ventricular wall that allowed the diastolic image to be divided into anterior and posterior halves of equal area. The mid point of this initial diastolic axis is systematically bisected by a series of radii 45° apart. This then creates a diastolic radial axis system of eight chords and their enclosed areas. Maintaining this reference system fixed in space and superimposing the systolic endocardial outline permits segmental evaluation of the ventricle, either by chordal shortening or regional area shrinkage.

Thirty-two patients were evaluated once the normal range of contraction was established from 10 normal volunteers. Twenty patients with coronary artery disease but without remote infarction had no difference in contraction pattern from that of the volunteers. Twelve patients had remote transmural infarction evidenced by abnormal Q waves. Six patients with anterior infarction showed impaired regional motion in anterior and anteroseptal regions, and six patients with inferior infarction showed impaired motion in posterior and lateral regions (Fig. 4 and 5). In conducting a parallel computer analysis of angiocardiograms in these 12 patients, two dimensional echocardiography proved as sensitive as angiography for detection of regional contraction defects: Each technique identified 10 of 12 patients correctly. These further observations confirm that two dimensional echocardiography can be used systematically to study regional wall motion abnormalities in patients with remote as well as acute myocardial infarction.

Surgical implications: The use of two dimensional echocardiography to characterize regional areas of abnormal contraction is in its nascent stage. Information gleaned from M mode techniques such as diastolic thinning, failure of appropriate systolic thickening and change of echocardiographic character within the wall producing acoustically "hard" areas, have only begun to be explored by two dimensional echocardiography (Fig. 6). The technique ultimately has the potential not only for identifying the presence of wall motion abnormalities, but also for quantifying their extent on a global basis and for assessing their reversibility. Thus, the unusually thinned echo-dense noncontractile region, which is probably composed of scar tissue, is unlikely to have its function restored by bypass surgery, whereas a poorly contracting area of myocardium of normal diastolic thickness and wall character may indeed recover its function after the blood supply is restored. The potential of echocardiography in this regard will be the subject of many further explorations within the next few years.

Special Complications of Myocardial Infarction

Ventricular aneurysm: Ventricular aneurysm (defined as an abnormal diastolic outpouching of the normal ventricular cavity) has long been recognized by M mode echocardiography. In a typical examination with the transducer in a standard location, a scan of the left ventricle from base to apex shows that the cavity expands or fails to taper as the region of the papillary muscles is approached. This finding is highly associated with the presence of left ventricular aneurysm. Many, but not all, left ventricular aneurysms fall within the path of a standard M mode scan. Thus, Weyman et al.[20] noted that in a series of 31 patients with angiographically proved left ventricular aneurysm, two dimensional echocardiography detected 100 percent of these defects whereas M mode studies were successful in detecting this abnormality 47 percent of the time. Typical examples of left ventricular aneurysm detected with two dimensional echocardiographic examinations are shown in Figure 7.

Ventricular pseudoaneurysm: In contrast to a true left ventricular aneurysms which is an abnormal outpouching of the infarcted left ventricular myocardium, a false aneurysm consists of cavitated clots that communicate with the left ventricular body through an area of myocardial rupture. In the patient who has not had antecedent cardiac trauma or surgery, myocardial infarction is the leading cause of pseudoaneurysm formation.[21] Unlike the orifice to a true aneurysm, which is wide and patent, the orifice to a false aneurysm is narrow. By virtue of this anatomic feature a false aneurysm is often detectable by echocardiography. Although the narrow orifice leading to the false aneurysm cavity was originally reported in M mode echocardiographic studies, two dimensional echocardiography greatly facilitates its recognition[22,23] (Fig. 8). Detection of a false aneurysm is more than an academic question

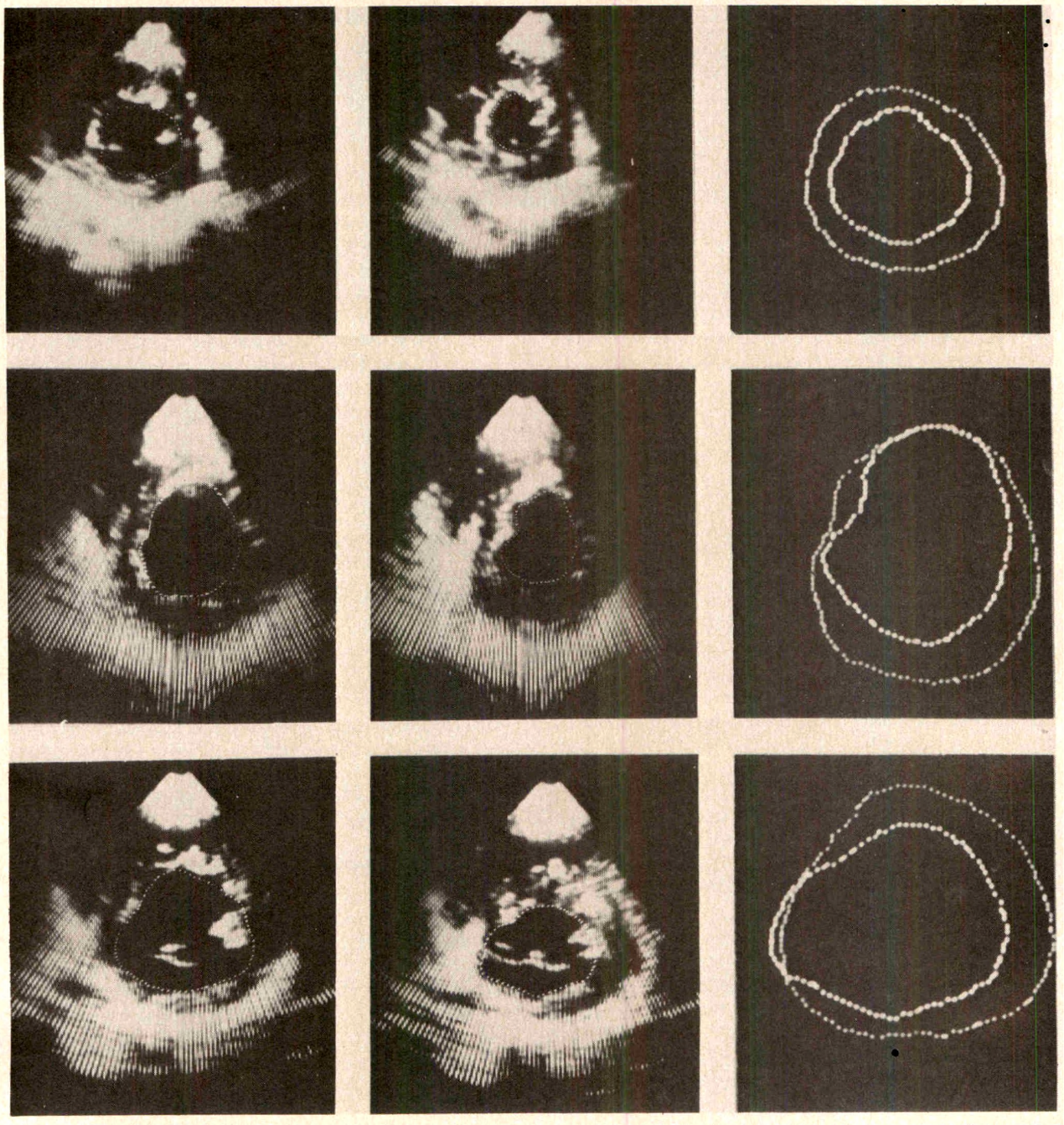


FIGURE 4. End-diastolic and end-systolic short axis images and computer regenerated outlines from a normal subject (**top**), a patient with anteroseptal myocardial infarction (**middle**) and a patient with inferior myocardial infarction (**bottom**).

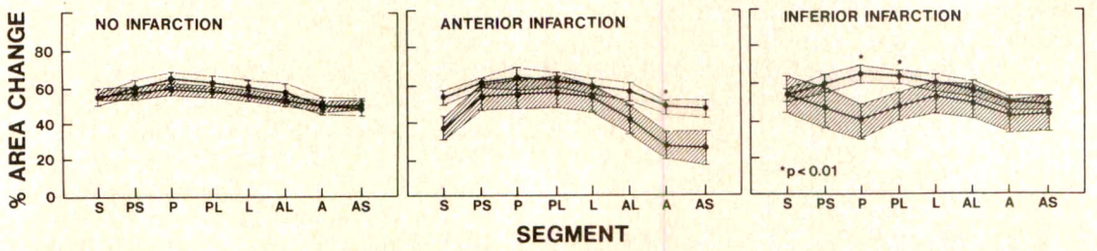


FIGURE 5. Plots of regional area shrinkage in 20 patients with no antecedent myocardial infarction and in two patient subgroups who had anterior or inferior myocardial infarction (see text). Abbreviations as in Figure 3.

because a false aneurysm is prone to fatal myocardial rupture, a complication very rarely encountered in a true left ventricular aneurysm. Moreover, it is readily amenable to surgery, which remains the treatment of choice. Thus, echocardiography, particularly with the two dimensional technique, is a key examination in the patient with an abnormally bulging radiographic cardiac silhouette after myocardial infarction. Because the primary clue to distinguishing true and false aneurysm depends on recognition of the narrowed orifice, a false aneurysm will not be suspected using standard chest roentgenograms.

Papillary muscle dysfunction and rupture: Mitral regurgitation may arise from anatomic or functional derangements of the papillary muscles. Papillary muscle dysfunction is most commonly caused by ischemia or

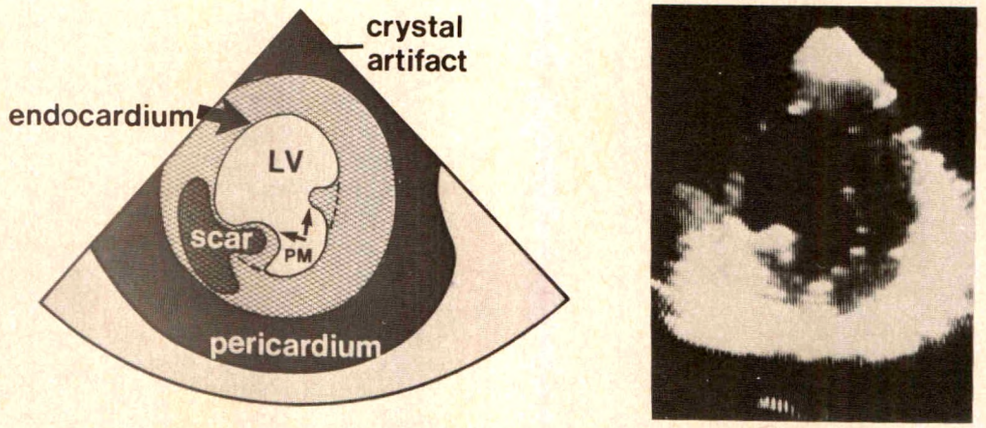


FIGURE 6. Short axis view of the left ventricle shown schematically and the actual image showing unusually hard echoes from the posteroseptal region in a patient with remote inferior myocardial infarction. These hard echoes correspond to the echo densities previously reported on M mode echocardiography. It would be difficult to gain access to the echo-dense region in this figure with the standard M mode approach. LV = left ventricle; PM = papillary muscles.

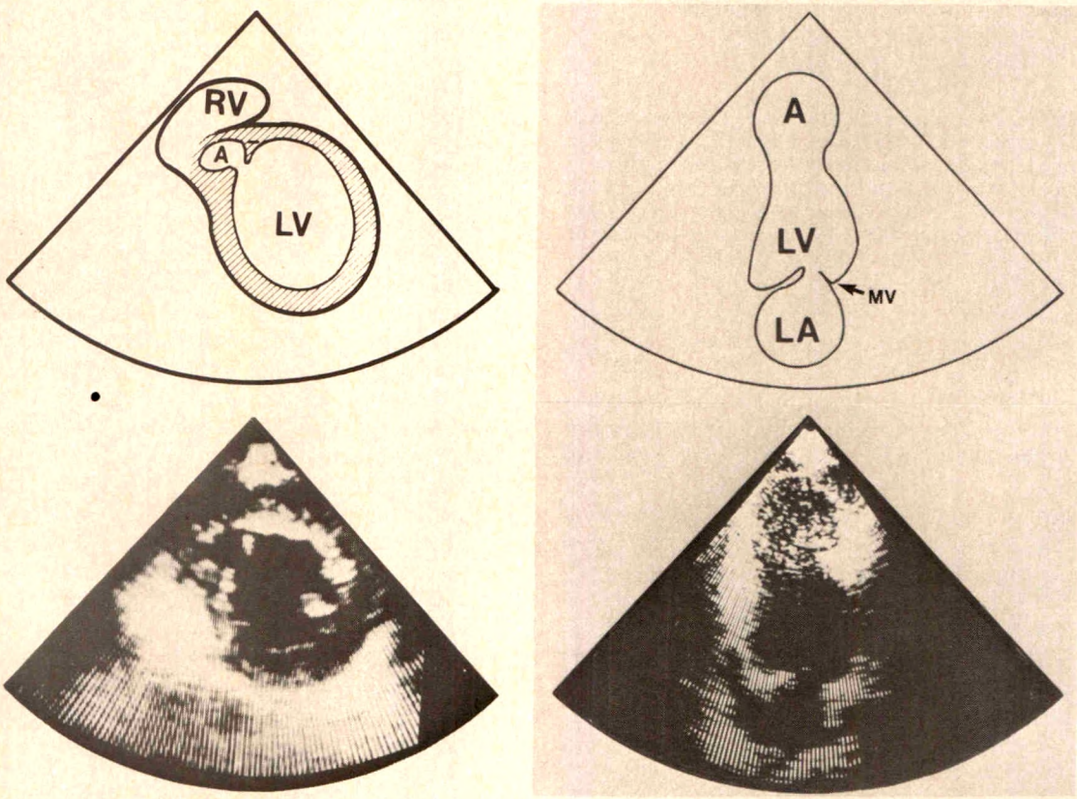
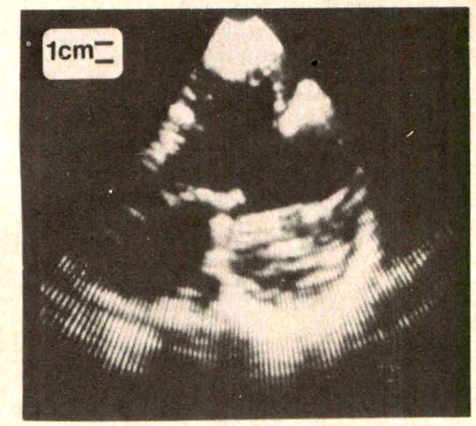


FIGURE 7. Examples of left ventricular aneurysm. **Left,** aneurysm of the interventricular septum in a patient with remote anterior myocardial infarction. This type of aneurysm is more likely to be missed on M mode scanning than is an apical aneurysm. **Right,** apical left ventricular aneurysm seen with an apical view on two dimensional echocardiography. The cloud of echoes within the aneurysmal chamber suggests a possible left ventricular thrombus. A = aneurysm; LA = atrium; LV = left ventricle; MV = mitral valve; RV = right ventricle.



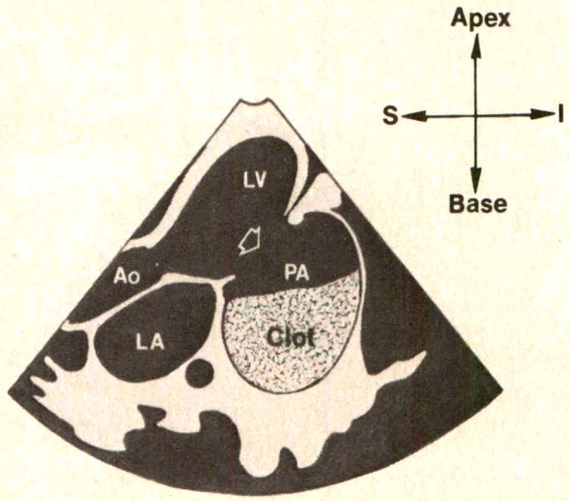


FIGURE 8. Top, two dimensional echocardiogram in apical two chamber projection of a patient with a pseudoaneurysm of the left ventricle. **Bottom,** schematic drawing of the orientation of the cardiac chambers and the pseudoaneurysm (PA). Ao = aorta; I = inferior; LA = left atrium; LV = left ventricle; S = superior. (Figure kindly supplied by Dr. M. Kotler and reprinted from Catherwood et al.[23] by permission of the American Heart Association, Inc.)

infarction which leads to asynergic contraction of the muscles, or by ventricular dilatation or aneurysm that produces sufficient malalignment to result in mitral regurgitation.

In a series of 14 patients with papillary muscle dysfunction,[24] two abnormal patterns of mitral valve closure were identified with two dimensional echocardiography: Three patients showed *mitral valve prolapse* associated with inferoposterior wall akinesia and increased tissue echo density consistent with papillary muscle fibrosis; nine patients with ventricular enlargement or aneurysm had *apically displaced mitral leaflet coaptation,* and the remaining two patients had both of these patterns.

Papillary muscle rupture is a devastating complication of acute myocardial infarction. It produces mitral regurgitation, which acutely imposes a volume overload on the left heart chambers. The magnitude of the volume load depends on the exact location of papillary muscle rupture. It is usually suspected from the sudden appearance of a loud systolic murmur, which may be impossible to distinguish at the bedside from the murmur of a ruptured interventricular septum (see later). If a head of a papillary muscle rather than an entire papillary muscle ruptures, it is possible that the patient can survive and undergo diagnostic evaluation that will allow its detection. As with ruptured chordae tendineae, this condition will lead to a flail anterior or posterior mitral leaflet; a flail valve can be readily appreciated on two dimensional echocardiography because one of the mitral leaflets swings freely into the left atrial cavity during ventricular systole[25] (Fig. 9).

Ventricular septal rupture: A ruptured flap of interventricular septum, showing an unusual pattern of motion, has been detected with M mode echocardiography in a patient with acute anteroseptal myocardial infarction.[26] Patients with this problem have also been reported to have, on average, an enlarged right ventricular internal dimension.[27] Direct visualization of loss of septal continuity is unlikely to be detected with M mode echocardiography because the septal rent may be irregular and obliquely located relative to the echographic beam passage from a parasternal or precordial transducer location. Nevertheless one such case has been reported.[28] In one instance[29] of a patient with documented postinfarction ventricular septal defect, the septum appeared split into two layers separated by an echo-free zone, which represented an obliquely passing communication from the left to the right ventricle.

Two dimensional echocardiography allows more complete inspection of the interventricular septum. With use of an apical four chamber view in which the length of the septum was delineated, three consecutive patients with ventricular septal rupture in the course of acute anterior infarction were identified.[30] In two of the three this was imaged as an oblique rent from the distal left ventricle to the proximal right ventricle, while in the third patient a large orifice was evident in the distal septum. Although postinfarction ventricular septal defect has not been frequently reported, it is anticipated that additional reports will appear as two dimensional equipment becomes more widely used in coronary care units and greater sophistication develops in exploring the integrity of the interventricular septum from different transducer locations.

Other complications of myocardial infarction: Two dimensional echocardiography offers the potential for making diagnostic decisions regarding other complications of myocardial infarction. Clots can be detected in relation to immobile areas of infarcted myocardial wall; pericardial effusion can be documented in the postinfarction patient with pericarditis. The latter is one of the applications in which M mode echocardiography is still quite valuable. In patients with inferior myocardial infarction in whom a pericardial friction rub and elevated neck veins develop, the distinction between right ventricular infarction and postinfarction pericarditis with cardiac tamponade accounting for

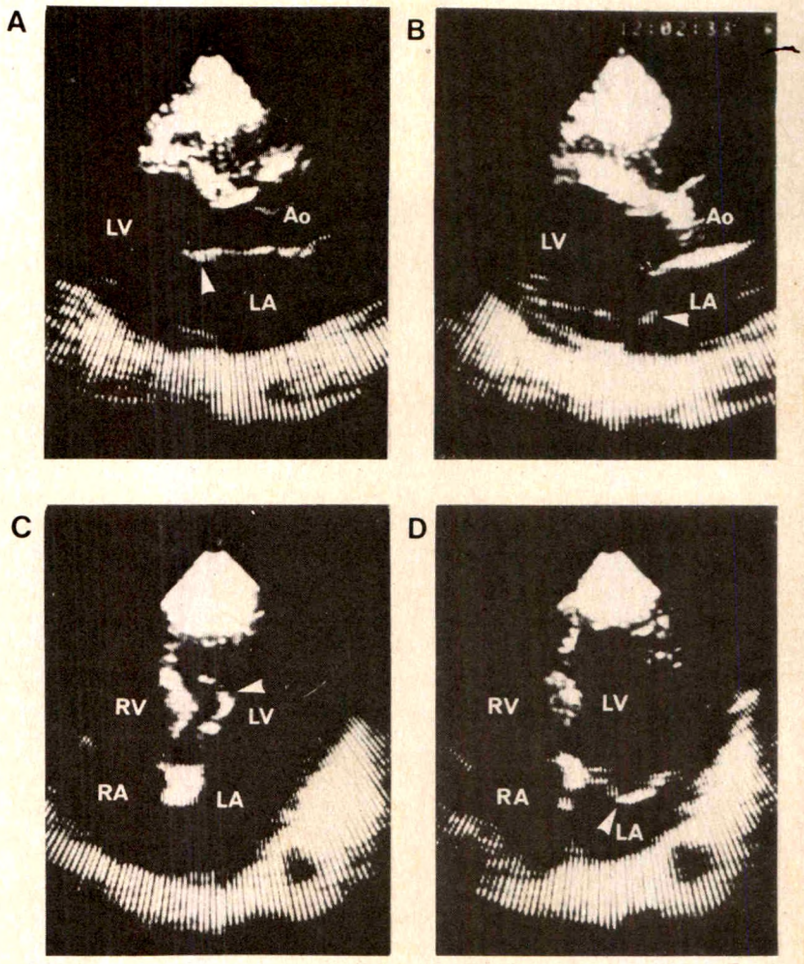


FIGURE 9. Example of flail mitral valve imaged with two dimensional echocardiography. The **upper two panels** demonstrate precordial long axis views of the left ventricle during diastole (**A**) and systole (**B**) showing the anterior mitral leaflet (**arrow**) swinging back into the left atrium (LA) during systole. The **lower two panels** are apical four chamber views that further demonstrate the abnormal motion of the anterior mitral leaflet (**arrow**), freely flailing into the left ventricle (LV) during diastole (**C**) and into the left atrium during systole (**D**). In addition, the apical views show a thickened echo-dense area of the high septum, a finding often associated with a flail anterior mitral leaflet. Ao = aorta; RA = right atrium; RV = right ventricle.

impaired right ventricular filling can be aided by echocardiography. Not all patients who manifest a pericardial friction rub in the course of myocardial infarction have significant pericardial effusion. In the absence of detectable effusion cardiac tamponade would be a very unlikely complication of acute myocardial infarction. Patients with tamponade not only show signs of effusion, but also are very likely to show signs of right ventricular compression. In contrast, regional dilatation of the right ventricle has been reported in right ventricular infarction if the involved area is traversed by the echographic beam.[31,32]

Advantages and Limitations of Two Dimensional Echocardiography in Myocardial Infarction

Two dimensional echocardiography offers distinct advantages for evaluating myocardial structure and function in myocardial infarction not currently available by other methods. First and foremost, if offers the most comprehensive information of any noninvasive imaging technique. One can appreciate from a single bedside examination not only myocardial structure and function, but also the area around the heart and the function of the cardiac valves. In addition, the resolution of detail obtainable with echocardiography is superior to that of any other noninvasive imaging modality. The relatively high degree of resolution is particularly useful in detecting special complications of infarction that can affect small and highly localized anatomic regions of the ventricle, such as papillary muscle dysfunction and formation of intramural thrombi. Another advantage of echocardiography in this setting is that it can be repeated, if necessary, multiple times on a daily basis without the concern of exposing the patient to ionizing radiation.

The principal limitation of echocardiography is its inability to obtain high quality images more than 60 to 80 percent of the time, depending on the investigator and the patient population. Although this difficulty is in part being overcome through improved techniques of examination using different approaches to imaging of the heart, further development of instrumentation will be necessary to achieve a success rate with ultrasound comparable with that of radionuclide imaging techniques.

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Thallium-201 Versus Technetium-99m Pyrophosphate Myocardial Imaging in Detection and Evaluation of Patients With Acute Myocardial Infarction

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Thallium-201 myocardial imaging is of value in the early detection and evaluation of patients with suspected acute infarction. The extent of a thallium defect in an initial myocardial image may have important prognostic value. Tomographic imaging techniques hold promise for increased diagnostic sensitivity and more accurate quantitation of both infarcted and residual viable myocardium. Thallium imaging may have a special value in characterizing patients with cardiogenic shock and in detecting patients at risk for subsequent infarction or death or both, before hospital discharge.

Approximately 95 percent of patients with transmural or nontransmural myocardial infarction can be detected with technetium-99m pyrophosphate myocardial imaging if the imaging is performed 24 to 72 hours after the onset of symptoms. Pyrophosphate imaging has been useful in localizing the site and determining the extent of acute myocardial infarction. The "doughnut" pattern is associated with a relatively large incidence of subsequent congestive heart failure and death. However, the clinical utility of this information is limited because it is usually not available when it is most needed, on admission to the coronary care unit. Pyrophosphate imaging may have an important role in the evaluation of patients during the early follow-up period after hospital discharge from an episode of acute infarction. The finding of a persistently positive pyrophosphate image suggests a poor prognosis and is associated with a relatively large incidence of subsequent myocardial infarction and death.

Both thallium-201 and technetium-99m pyrophosphate myocardial imaging are increasingly being used to evaluate patients with acute myocardial infarction. Since the introduction of these tracer techniques in the mid 1970s, they have excited the interest of the clinical investigator and have rapidly been applied in university and community hospitals throughout the world. In this report we review their current status in detecting and evaluating patients with acute myocardial infarction and to place these methods in perspective as we enter the 1980s.

Thallium-201 Myocardial Imaging

Physiologic and anatomic principles: Thallium-201 is taken up by normal myocardial cells in proportion to blood flow.[1] Within the physiologic range of blood flow the extraction of thallium by the myocardium is approximately 88 percent.[2] Only at the extremes of the physiologic range of myocardial flow does the relation of thallium uptake by the myocardial cell and blood flow deviate. At low flows relatively more and at high flows relatively less thallium is extracted from the blood.

In normal persons, thallium-201 is relatively uniformly distributed throughout the myocardium. The normal myocardial thallium image may show an area of relatively diminished uptake at the apex, because the apex is normally thinner than the left ventricular free wall and septum.[3] The right ventricle is usually not well defined in a left anterior

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oblique thallium myocardial image obtained at rest because the mass and blood flow per gram of the right ventricle are less than those of the left ventricle. However, during exercise, tachycardia and acute pulmonary hypertension (conditions that result in an increase in right ventricular blood flow and mass), the right ventricle can be detected easily.[4]

Areas of myocardial ischemia or infarction, or both, can be detected on thallium-201 myocardial imaging by the relative absence of tracer uptake in a region of the myocardium. Ischemia or infarction, or both, can be detected immediately after experimental coronary arterial ligation because blood flow, and hence thallium uptake, will be diminished. Ischemia can be differentiated from infarction by serial myocardial imaging and quantification of the redistribution of thallium-201.[5] If myocardial imaging is repeated 1 to 6 hours after the injection of tracer, normal areas of myocardium will lose thallium activity. In contrast, areas of myocardial ischemia will have a relative increase in activity as thallium distributes in time according to myocardial mass. Areas of permanent myocardial damage after myocardial infarction will show diminished thallium-201 activity in both initial and delayed serial images.

The location of the defect in a thallium-201 image is also of interest because it can be used to predict the underlying anatomic disease.[6] For example, defects in thallium uptake in the anterior apical region in an anterior view or defects in the area of the interventricular septum in the left anterior oblique image indicate significant disease of the left anterior descending coronary artery. Lesions of this artery above the first septal perforator can be distinguished from those below this branch. Lesions above this branch can be detected by the finding of a defect in thallium-201 uptake involving the septum in a left anterior oblique view; lesions below this branch involve the anterior apical region in an anterior view, but not the septum in the left anterior oblique view. This differentiation may be of clinical importance because it has recently been pointed out that lesions of the left anterior descending coronary artery above the first septal perforator are associated with a large incidence of ventricular fibrillation or sudden cardiac death, or both.[7] Lesions in the right coronary artery may be detected by finding a defect on the diaphragmatic surface or apex in the right anterior oblique view; however, occasionally, because of anatomic variation, lesions of the left circumflex coronary artery may also project there. Lesions of the latter artery can be detected by the finding of a tracer defect on the high lateral wall in a left anterior oblique or left lateral image. These physiologic and anatomic principles provide the basis for the use of thallium-201 myocardial imaging in the detection and evaluation of patients with acute myocardial infarction.

Patients with suspected myocardial infarction or ischemia: Thallium-201 myocardial imaging has been shown to be of value in the early detection and evaluation of patients with suspected acute myocardial infarction. Patients with a diagnosis of "rule out myocardial infarction" remain a major problem in most medical centers. Approximately half of the patients admitted to the coronary care unit for suspected infarction are shown not to have infarction. These patients include those with unstable angina pectoris or coronary insufficiency, patients with previously known ischemic heart disease and acute chest pain of noncardiac origin, and those with chest pain of noncardiac origin without underlying ischemic heart disease. If techniques could be developed to triage accurately patients with suspected acute myocardial infarction, great savings in cost and increased effectiveness of diagnosis and therapeutic interventions could be realized. Although thallium-201 myocardial imaging cannot be expected to solve this problem entirely, there is accumulating information to suggest that it may be of value under special circumstances.

During the early hours of myocardial infarction, the electrocardiogram may not be diagnostic of acute myocardial infarction. Similarly, serum creatine kinase may not be elevated for the first few hours after myocardial damage. In these early hours serial thallium-201 myocardial imaging may be of value.[8] If a defect in thallium uptake is seen in an initial myocardial image, myocardial infarction should be suspected and the patient admitted to the coronary care unit for routine monitoring and therapy of acute myocardial infarction. If the defect in thallium uptake can no longer be detected on reimaging 2 to 3 hours later, acute myocardial ischemia without infarction or only minor infarction should be suspected. Patients with these findings should also be admitted to the coronary care unit, but mobilization and the application of diagnostic and therapeutic interventions for myocardial ischemia can be accelerated. In patients who have normal thallium myocardial uptake on both initial and serial imaging, myocardial ischemia or infarction is less likely, and chest pain of noncardiac origin should be considered. One limitation of this approach is that patients with prior myocardial infarction and scarring may have residual defects in thallium uptake indistinguishable from defects secondary to acute infarction even with serial imaging. A documented history of prior myocardial infarction should alert the clinician to this possibility.

Patients with right ventricular infarction: Another limitation of this approach is that right ventricular infarction may not be detected and a misdiagnosis of chest pain of noncardiac origin may be made because the right ventricle is often not seen in a thallium-201 image obtained at rest. To eliminate the possibility of right ventricular infarction as a cause of the patient's symptoms, a gated blood pool image can be obtained. If right ventricular infarction is present, it will be manifested by a poorly contracting large ventricle with or without concomitant left ventricular dysfunction.[9] In our experience, right ventricular infarction can often be diagnosed with blood pool imaging before the development of characteristic hemodynamic findings. Early in the course of right ventricular infarction, right ventricular filling pressure may be only slightly elevated although the right ventricle is markedly dilated because this chamber is more compliant than the left ventricle.

Only after volume challenge or loading will the right ventricular filling pressure increase in disproportion to left ventricular filling pressure. If both right and left ventricular infarction can be excluded within the first few hours of onset of symptoms, patients could undergo appropriate diagnostic studies more quickly to determine the cause of the chest pain without the expense and stigma often associated with admission to the coronary care unit.

Early diagnosis of acute myocardial infarction: Once a patient is in the coronary care unit, thallium-201 myocardial imaging has proved a highly sensitive technique to detect the presence of infarction. Wackers et al.[10,11] in an early study in Amsterdam found that 100 percent of patients with either transmural or nontransmural infarction could be detected by the finding of a defect in thallium uptake in the initial image made within 6 hours of onset of symptoms. With increasing time from the onset of symptoms, the sensitivity for detecting infarction, especially nontransmural infarction is diminished. In the series of Wackers et al. the sensitivity for detecting infarction was 58 percent after 24 hours.

Because sensitivity decreases with time, prompt application of thallium-201 is important for this approach to be effective. The 74 hour physical half-life of thallium-201 is long enough to permit storage of the tracer in the hospital nuclear pharmacy for emergency use. In large metropolitan areas the tracer is increasingly accessible from centralized pharmacies.

Diagnosis of remote infarction: Although the sensitivity for detection of infarction by thallium-201 myocardial imaging diminishes with time, the detection of remote infarction remains greater than that for the electrocardiogram. In an early study of 101 patients with a documented old myocardial infarction (from 3 months to 10 years), a definite diagnosis could be made in 61 patients using electrocardiographic criteria and in 76 by the finding of a defect in a thallium image obtained at rest ($p < 0.01$).[12]

Predicting prognosis: Thallium-201 myocardial imaging may also be of value in predicting prognosis. The extent of the thallium defect has been shown to correlate with pathologically determined infarct size and with the contrast angiographic extent of asynergy.[13,14] Thallium defects have been found in more than 90 percent of patients with asynergic segments greater than 60 percent of the left ventricular circumference.[15] The extent of the thallium defect in an initial myocardial image in the coronary care unit has also been shown to have important prognostic value and to be a better prognostic indicator of subsequent survival than the extent of left ventricular dysfunction in a blood pool image.[13] The extent of a thallium defect may be defined by relatively simple computer programs. The myocardial image can be circumscribed by a light pen or edge detection routine and radi drawn from the center of activity to the perimeter of the image. In a normal person there is relatively uniform activity along each radius. This information can be displayed graphically from 0 to 360°. In patients with myocardial ischemia or infarction, or both, the extent of the defect in thallium uptake can be quantitated by determining the number of degrees around the perimeter with decreased thallium-201 activity. With this technique it is possible to define a group with a relatively high mortality rate after myocardial infarction and one with a low risk of subsequent mortality.[13]

Assessing extent of myocardial damage: The extent of myocardial damage can also be assessed with tomographic imaging techniques.[16,17] New collimators have been developed that can be applied to standard scintillation cameras to obtain tomographic images by computer reconstruction techniques. Tomographic imaging techniques have been used to estimate the extent of experimental myocardial infarction and when they are used an excellent correlation has been found between pathologically determined infarct size and estimated infarct size[18] despite the inherent "pincushion" distortion with these collimators. Although experience with tomographic imaging in patients with acute myocardial infarction is limited, this technique should allow increased diagnostic sensitivity for the detection of infarction as well as the capacity for more accurate quantitation both of the infarcted and residual viable myocardium. (Fig. 1 and 2).

Patients with cardiogenic shock: Thallium-201 myocardial imaging may also be of value in assessing patients with cardiogenic shock. For example, patients with cardiogenic shock due to massive left ventricular damage will have an extensive defect in left ventricular thallium-201 uptake, often involving greater than 40 percent of the left ventricular circumference. In those with persistence of a defect of this magnitude on serial imaging several hours later, the prognosis is poor regardless of therapy because the amount of residual viable myocardium is often insufficient to maintain adequate pump function over time. Redistribution of thallium into the area of the initial defect in tracer uptake suggests reversible myocardial ischemia and the possibility of improvement by intraaortic balloon pumping and possibly by coronary bypass graft surgery. Patients with cardiogenic shock and an electrocardiographic pattern of an inferior myocardial infarction may have massive left ventricular damage demonstrated by thallium imaging. Normal or almost normal left ventricular uptake of thallium suggests massive right ventricular damage. The prognosis in patients with these findings is good if the damage is limited to the right ventricle and appropriate therapy, such as plasma volume expansion, is instituted.

Evaluation of patients for coronary bypass surgery: Thallium-201 myocardial imaging is also of value in detecting areas of myocardium at risk during exercise for subsequent myocardial infarction and therefore for possible coronary arterial bypass graft surgery.[12] Exercise electrocardiographic testing before hospital discharge after myocardial infarction has been shown to be useful in detecting patients at high risk for subsequent infarction or death, or both.[19] The appearance on exercise of a new tracer defect outside the area of infarction detected in a thallium-201 myocardial image

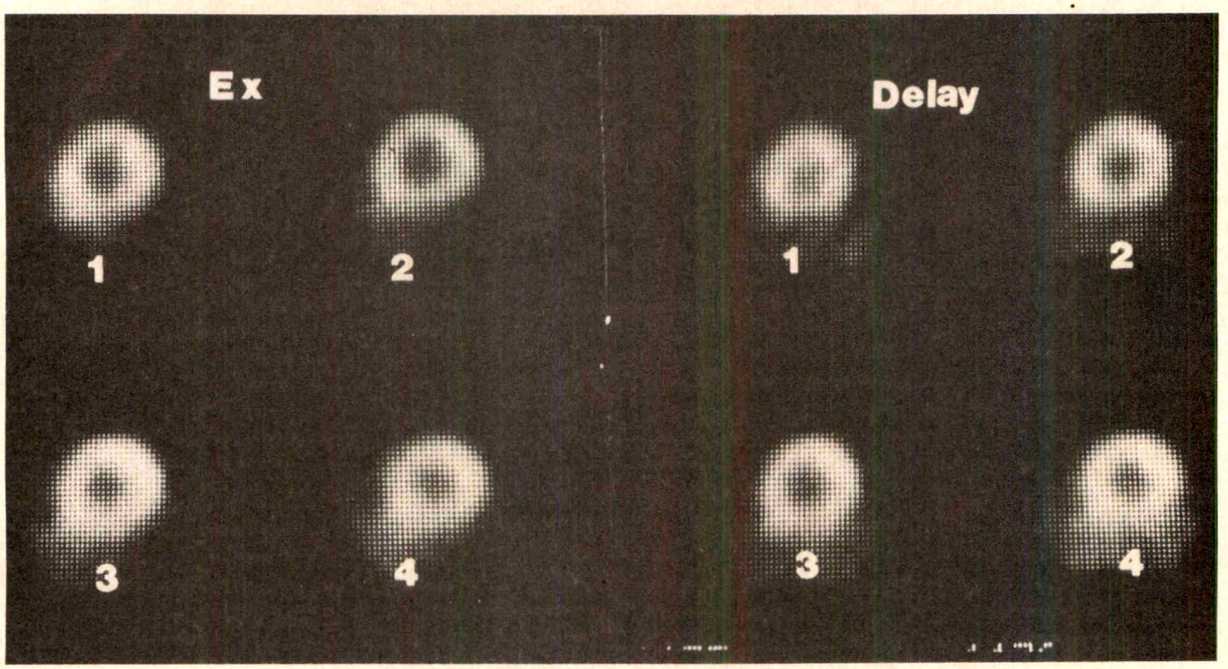


FIGURE 1. Tomographic thallium-201 myocardial images (1 to 4) in a patient with normal coronary arteries. Note the relatively uniform thallium-201 uptake in both the exercise (Ex) and delayed images (3 hours later).

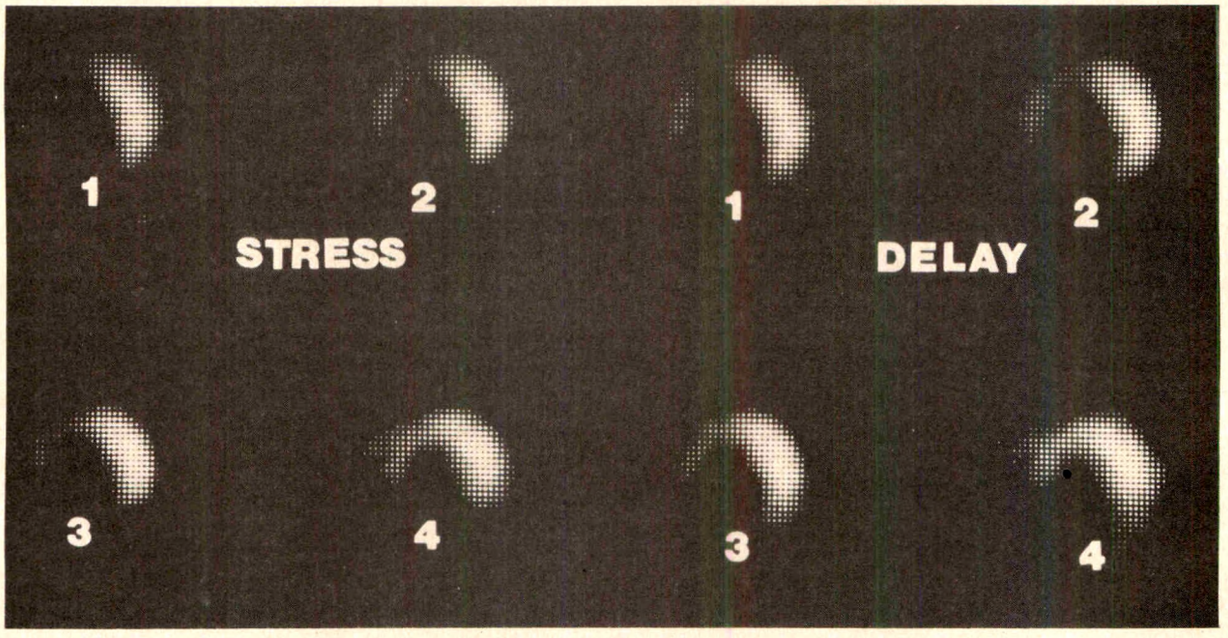


FIGURE 2. Tomographic thallium-201 images in a patient with a history of myocardial infarction. **Left,** the images after submaximal stress; **right,** the delayed images (3 hours later). Note that the area of decreased tracer uptake is similar in both the stress and delayed images, confirming that the area of decreased tracer uptake is due to infarction rather than ischemia.

obtained at rest indicates a "risk" segment (that is, an area of viable myocardium served by a significantly narrowed coronary artery). In a recent study more than 80 percent of "risk" segments confirmed on coronary angiography could be detected with exercise thallium-201 myocardial imaging.[20] Although experience is still limited, our current procedure is to perform rate-limited exercise electrocardiography and thallium-201 myocardial imaging before hospital discharge after an episode of myocardial infarction. Patients who do not exhibit evidence of myocardial ischemia on electrocardiography and do not exhibit a new defect in thallium uptake on exercise are assumed to be at low risk for subsequent infarction or cardiac death, or both, and are discharged to normal activity after convalescence. Patients who exhibit evidence of myocardial ischemia on

electrocardiography or show evidence of a new defect on thallium myocardial imaging are considered for early coronary arteriography in order to detect candidates for early bypass graft surgery. To determine whether this approach is correct will require further experience and carefully controlled trials.

Technetium-99m Pyrophosphate Imaging

Physiologic and anatomic principles: Myocardial infarction can also be detected with the uptake of technetium-99m pyrophosphate within an area of acute infarction.[21] This is in contrast to thallium-201 myocardial imaging in which infarction is recognized by an absence of tracer uptake. Since its introduction in 1974 by Bonte et al.[21] technetium-99m pyrophosphate myocardial imaging has found wide clinical application. Although the exact mechanism of technetium-99m pyrophosphate uptake by infarcted myocardium is still being investigated, the weight of evidence suggests that the major mechanism is the formation of complexes with tissue calcium stores within the injured cell.[22] Technetium-99m pyrophosphate may also form complexes with damaged myocardial proteins and other macromolecules, but this may not be as important as the binding to tissue calcium. Residual myocardial blood flow is also of direct importance because, if there is no residual flow, tracer cannot be delivered to the area of infarction. This is evident from the pattern of pyrophosphate uptake in patients with massive myocardial damage in which the central necrotic area with low residual flow fails to take up tracer, whereas the surviving border zone with residual collateral flow avidly takes up tracer resulting in a "doughnut" pattern.

Areas of myocardial infarction can be detected approximately 12 hours after the onset of symptoms. However, imaging at this time will result in a relatively low sensitivity for detection of infarction. Maximal sensitivity for detection of infarction is achieved 24 to 72 hours after the onset of symptoms.[23] After 1 to 2 weeks, pyrophosphate uptake by the myocardium is usually not detected but in some patients a positive image may persist for several weeks or months. It is important to wait at least 90 minutes and preferably 3 hours after injection of pyrophosphate before imaging. Imaging performed earlier than 90 minutes after injection may result in a low specificity due to persistence of blood pool activity and the appearance of diffuse uptake, which may be mistaken for a positive image. Wherever there is a question that apparent uptake is due to blood pool activity, further delayed views should be obtained for comparison. Several approaches have been used to grade pyrophosphate images. The most commonly used is that recommended by Willerson et al.[23] Scintigrams are graded from 0 to 4+: 0 = no activity; 1+ = minimal activity; 2+ = definite myocardial activity; 3+ = activity equal to bone activity; and 4+ = activity greater than bone activity. In this system scans with 2+ or greater activity are thought to suggest acute myocardial infarction.

Sensitivity of test for acute infarction: If imaging is performed during the optimal time, 24 to 72 hours after onset of symptoms of acute infarction, approximately 95 percent of patients with transmural or nontransmural infarction will be detected.[24] To obtain such a high sensitivity with a high specificity requires careful attention to imaging technique and the use of serial imaging. However, such high sensitivity for detecting infarction has not been a universal finding. For example, Lyons et al.[25] recently reported that 96 percent of patients with transmural infarction had pyrophosphate uptake, but in only 82 percent was the uptake localized. Similarly, 88 percent of patients with nontransmural infarction had pyrophosphate uptake but the uptake was localized in only 44 percent. A relatively large proportion of patients with chest pain, unstable angina pectoris, congestive heart failure or pericarditis, as well as patients studied after resuscitation, also had pyrophosphate uptake, but not a localized pattern. Therefore, if one requires a localized or focal pattern of uptake as the criterion for diagnosis of myocardial infarction, the sensitivity for detecting nontransmural infarction is relatively low, approximately 44 percent.

Several conditions are known to cause false positive pyrophosphate images. They include calcific valvular heart disease, left ventricular aneurysm with dystrophic calcification, inflammation or tumors of the breast, and disease of the chest wall or ribs. Cardioversion with skeletal muscle damage may also cause pyrophosphate uptake.[26]

Limitations of method: The major limitation of pyrophosphate imaging for detection of acute myocardial infarction is that in most instances the diagnosis has been established with serial electrocardiography and serum enzyme determination in 24 to 72 hours, the time of optimal pyrophosphate imaging. In the approximate one fourth to one third of patients with infarction in whom the diagnosis is still in doubt at 48 hours, pyrophosphate imaging is of limited value in view of the relatively low sensitivity for detecting nontransmural infarction if a localized pattern is required and the frequent occurrence of the conditions known to cause false positive images. Although only a relatively small proportion of patients with infarction will be detected during the early hours of infarction with pyrophosphate imaging, imaging 5 hours after infarction may have some value. Recent experimental studies[27] suggest that the early appearance of pyrophosphate uptake indicates reperfusion injury due to reversible coronary arterial occlusion with more rapid delivery of flow to the infarcted region than would occur by collateral channels over 48 to 72 hours in animals with a completely occluded vessel This approach may therefore be of value in detecting patients with infarction due to coronary arterial spasm.

Localizing the site and extent of infarction: Pyrophosphate imaging has also been useful in localizing the site and determining the extent of acute myocardial infarction. For example, right ventricular infarction has been diagnosed by the finding of a characteristic pattern of pyrophosphate uptake in the left anterior oblique image.[28] As previously pointed out, patients with the electrocardiographic pattern of an inferior myocardial infarction may have a spectrum of anatomic damage involving the left or the right ventricle, or both. Al-

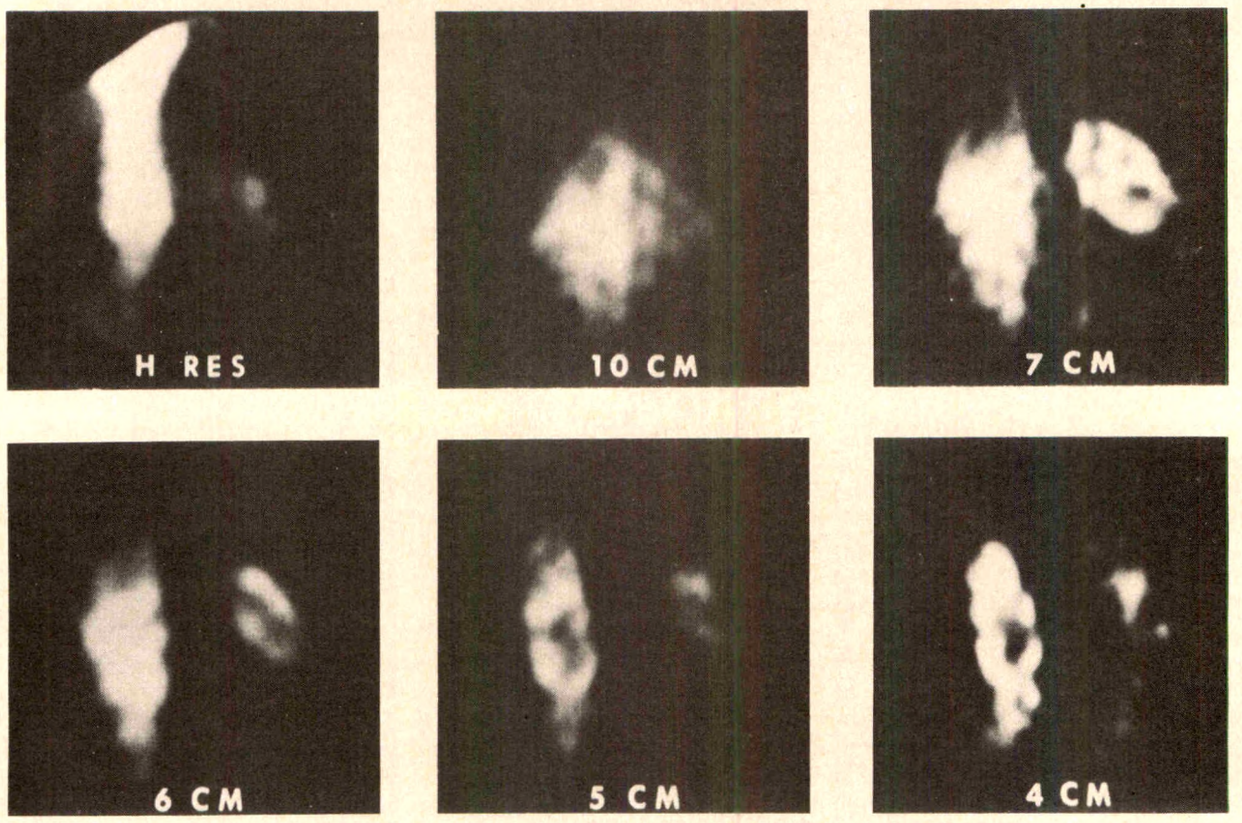


FIGURE 3. Technetium-99m pyrophosphate tomographic myocardial imaging. A standard planar image using a high resolution (H RES) collimator is shown in the **upper left panel** and tomographic cuts in the same patient at 10, 7, 6, 5 and 4 centimeters (CM). The tomographic images provide a better estimate of the extent of infarction than does the standard planar image.

though this differentiation has important therapeutic and prognostic implications, the information provided by pyrophosphate imaging is often too late to be of therapeutic importance.

The extent of pyrophosphate uptake has also been correlated with the extent of myocardial infarction using standard imaging techniques. Good correlations between the extent of infarct-avid agents and the extent of acute anterior transmural myocardial infarction have been found.[29,30] Less satisfactory correlations have been found in patients with inferior or posterior myocardial infarction because of inadequate projection of the area of damage when standard imaging techniques are used. Recently, this limitation has been overcome using tomographic imaging techniques[31] (Fig. 3). Excellent correlations between the extent of infarction determined pathologically and the extent of pyrophosphate uptake have been found for transmural infarction in all locations using tomographic techniques. Precise correlation between the extent of pyrophosphate uptake and infarction in patients with nontransmural infarction is less satisfactory because of the presence of the pattern of diffuse uptake in some patients. Nevertheless, some correlation with the extent of damage can be found even in patients with nontransmural infarction.

The prognosis in patients with myocardial infarction depends on the extent of myocardial damage, both new and old. Patients with an old anterior transmural myocardial infarction may present with an acute inferior infarction or nontransmural infarction. The extent of pyrophosphate uptake and, similarly, creatine kinase release will reflect only the acute damage in these situations. Implications as to prognosis based on infarct size determined from techniques that reflect only acute damage must of necessity be misleading. Under these circumstances techniques that reflect total myocardial damage will be of greater value. Total myocardial damage can be assessed from the extent of a defect in thallium-201 uptake or from the extent of ventricular dysfunction on gated blood pool imaging. For example, in one early study[32] no significant difference could be found in creatine kinase release between survivors of infarction and those subsequently dying, whereas there was a significant difference in an index that reflected total myocardial damage, such as left ventricular ejection fraction and percent of the left ventricular wall that was akinetic on blood pool imaging.

Significance of "doughnut" imaging pattern: Despite these limitations pyrophosphate imaging may provide important prognostic information. The "doughnut" pattern has been found in patients with massive anterior transmural infarction. The essentially clear area without pyrophosphate uptake indicates se-

verely necrotic myocardium with inadequate myocardial blood flow for delivery of tracer. In one study[33] of 71 patients with acute anterior myocardial infarction, 45 were shown to have a doughnut pattern and 26 a "focal" pattern of uptake. Peak creatine kinase release in those with a doughnut pattern was 660 units compared with 344 units in those with a focal pattern ($p < 0.05$). Of the patients with a doughnut pattern, 67 percent had congestive heart failure and 9 percent died, whereas among those with a focal pattern, only 35 percent had congestive heart failure and none died. Similarly, Ahmad et al.[34] found late complications in all patients with a doughnut pattern of pyrophosphate imaging compared with only 43 percent of patients with a focal pattern of uptake and 12 percent of those with a diffuse pattern. The post-hospital mortality rate was 83 percent in those with a doughnut pattern, 6 percent among those with a focal pattern and 0 percent among those with a diffuse pattern. Although these early data are encouraging and identification of high risk subsets after myocardial infarction is clearly of great importance, a larger experience will be required to determine if the doughnut pattern provides prognostic information over and above that obtainable by more routine clinical techniques, including creatine kinase release.

Persistently positive image after infarction: One circumstance in which pyrophosphate imaging appears to provide independent prognostic information not readily obtainable by other techniques is the occurrence of persistently positive image after infarction. Olsson et al.[35] recently reported on 109 patients in whom pyrophosphate imaging was performed a mean of 31 weeks after infarction; 61 patients (56 percent) had a positive pyrophosphate image and 48 (44 percent) a negative image. These patients were followed up for a mean of 50 weeks. In those with a positive pyrophosphate image 10 percent had recurrent myocardial infarction and 16 percent died compared with a 2 percent incidence rate for both myocardial infarction and for death in those with a negative image. They also noted an increased incidence of congestive heart failure and severe angina pectoris in those with a positive image.

The finding of a persistently positive pyrophosphate image after an episode of acute myocardial infarction may be due to unresolved calcium complexes within the infarcted region, dystrophic myocardial calcification or ongoing myocardial necrosis. In the past we tended to think of myocardial infarction as a sudden event healing in 6 to 8 weeks. More likely, many patients with infarction have islands of viable myocardium within the distribution of the "infarct." These islands of viable myocardium are supplied by collateral flow that, although adequate to preserve myocardium initially, may be inadequate over time and during periods of increased oxygen demands required during stress. Identification of this high risk subset with a persistently positive pyrophosphate image suggests the need for new therapeutic strategies.

Patients with unstable angina: A similar situation has been encountered in patients presenting with unstable angina pectoris.[36] Several groups have noted that approximately one fourth of patients with unstable angina pectoris but without serial electrocardiographic or serum enzyme evidence of acute myocardial infarction have a positive pyrophosphate image. Initially it was thought that a positive pyrophosphate image under these circumstances was a false positive image. However, recent studies suggested that a positive pyrophosphate image under these circumstances may represent subclinical myocardial necrosis. Small areas of myocardial necrosis are frequently seen at postmortem examination in patients with unstable angina pectoris dying of other causes and have been correlated with a positive pyrophosphate image. Olson et al.[36] reported on 199 patients with unstable angina pectoris without electrocardiographic or serum evidence of myocardial infarction; 67 (34 percent) had a positive and 132 (66 percent) a negative pyrophosphate image. Of those with a positive pyrophosphate image 21 percent had subsequent nonfatal myocardial infarction and 22 percent had cardiac death during a mean follow-up period of 35 weeks compared with a 3 percent incidence rate of nonfatal infarction and a 6 percent incidence rate of cardiac death in those with a negative image. It is possible that those with a positive pyrophosphate image had ongoing or sporadic episodes of myocardial necrosis similar to those of patients with cerebrovascular disease and ischemic attacks.

Identification of a high risk subset of patients with unstable angina has important therapeutic implications. For example, in those with a negative image with a low risk of subsequent infarction and death, conservative medical therapy appears justified, whereas in those with a positive image more aggressive therapy, possibly medical or surgical, seems indicated. Failure to separate high and low risk subsets in any trial of therapy in unstable angina may lead to an inability to show efficacy of a therapeutic intervention and may in part account for the failure of the multicenter trial of coronary arterial bypass graft surgery to show a significant effect of surgery on survival.[37]

Clinical Applications

Diagnostic protocol in thallium-201 imaging: We suggest that if, after routine clinical examination, electrocardiography and initial serum enzyme determination, there is a question as to the diagnosis of acute myocardial infarction in a patient without a previous history of infarction, serial thallium-201 imaging should be considered. This technique will be of special value when applied to patients without known previous ischemic heart disease who present to the emergency room with chest pain or symptoms suspicious of acute myocardial infarction within the first few hours of onset of symptoms. The finding of a defect in thallium-201 uptake suggests the presence of ischemic heart disease. If serial imaging 2 to 3 hours later demonstrates that the defect persists or enlarges, acute myocardial infarction should be suspected and the patient admitted for further observation. In patients with negative serial thallium-201 myocardial images but a high suspicion of infarction by clinical history, a blood pool image may

be obtained in both the right and left anterior oblique projections. The finding of a normal left ventricular ejection fraction and normal wall motion of both the right and left ventricles makes the presence of an acute infarction unlikely.

Protocol in high risk patients to evaluate therapy: In patients admitted to the coronary care unit with the diagnosis of acute myocardial infarction an initial thallium-201 myocardial image and quantification of the extent of thallium defect provide important prognostic information sufficient to assign patients to high or low risk subsets.[13] To evaluate the effectiveness of therapeutic interventions blood pool imaging should be considered.[38–40] Although not reviewed in this study, left ventricular ejection fraction determined with blood pool imaging is highly reproducible and correlates well with values obtained with standard contrast angiography. In patients with complicated myocardial infarction and cardiogenic shock a combination of thallium-201 myocardial imaging and blood pool imaging should be considered to identify those with massive irreversible left ventricular damage, whose prognosis is poor even with aggressive therapy, those with residual left ventricular ischemia or right ventricular damage and those whose cardiogenic shock is the result of a small strategically placed infarction (such as with rupture of a papillary muscle or of the interventricular septum).

Role of pyrophosphate imaging in the coronary care unit: Although there is undoubtedly still much to be learned from infarct-avid imaging, technetium-99m pyrophosphate imaging with standard imaging techniques will not find wide application within the coronary care unit. By the time the optimal sensitivity is obtained at 48 to 72 hours, the information concerning the presence of infarction and its location and extent is to a large degree superfluous. To be of clinical value, this information is necessary on admission to the coronary care unit. In those patients in whom the question of infarction is still unanswered at 48 to 72 hours and in those whose onset of symptoms is uncertain, pyrophosphate imaging may prove to be of value, but the relatively low sensitivity of detecting nontransmural infarction reported from several centers and the high but still imperfect specificity of the technique raises doubt as to its clinical utility even in these circumstances.

Does infarct-avid imaging with pyrophosphate have any role in the evaluation of patients with acute myocardial infarction? Pyrophosphate imaging may be useful in the detection of peri- and postoperative myocardial infarction.[41] If the early data of Olson et al.[35] can be confirmed in other centers, pyrophosphate imaging would also appear to have a most important role, not in the coronary care unit, but in the evaluation of patients seen during the early follow-up period after hospital discharge after an episode of acute infarction. The finding of a persistently positive pyrophosphate image suggests a poor prognosis and the need for therapeutic intervention, whereas the finding of a negative image appears to indicate a low risk subset of patients in whom high risk interventions should be applied cautiously, if at all. Similarly, the patient with unstable angina pectoris and a positive pyrophosphate image appears to have a different prognosis and to require more aggressive therapy than the patient with a negative image and an excellent prognosis.[36]

Future directions: As we enter the coming decade, thallium-201, technetium-99m pyrophosphate and blood pool imaging techniques will undoubtedly play an increasingly important role in detecting patients with ischemic heart disease, selecting high risk subsets for therapeutic interventions and evaluating the effects of therapeutic interventions, as well as providing further insight into the natural history of disease processes. New imaging techniques and improvements and developments of new radiopharmaceuticals will undoubtedly open new areas for clinical investigation. However, the challenge of the next several years is to apply more efficiently currently available techniques. We must determine where and when they are cost-effective and an aid in clinical decision-making as well as where and when they are superfluous, adding only to the cost of care without affecting clinical outcome. Although it is the role of the clinical investigator to provide this information, it is the role of the individual clinician to be satisfied that this information is available and reliable before he applies these techniques clinically. It is not enough that a new technique such as pyrophosphate myocardial imaging diagnoses the presence of myocardial infarction or estimates the size of myocardial infarction. To be clinically applicable and to justify the expense of the technique, the technique must provide information not obtained by less costly techniques and must result in clinical decisions affecting patient outcome that are otherwise not possible. If these conditions can be met, as we believe they will be, and if the techniques are intelligently applied, we can look forward to improved diagnosis and evaluation of patients with acute myocardial infarction.

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Value and Limitations of Two Dimensional Echocardiography In Assessment of Cardiomyopathy

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Primary myocardial diseases have traditionally been classified into congestive, hypertrophic and restrictive varieties. M mode echocardiography has proved extremely valuable in distinguishing congestive cardiomyopathy with major ventricular dilation and poor contractile performance from hypertrophic cardiomyopathy with predominant left ventricular hypertrophy (septum greater than posterior wall) and normal pump performance, and restrictive disorders with symmetric ventricular wall thickening and normal or diminished contractile function. The contributions of two dimensional echocardiography to the evaluation of patients with congestive or restrictive cardiomyopathy have been limited to certain specific situations, such as the recognition of left ventricular mural thrombi.

Twenty-five patients with hypertrophic cardiomyopathy were studied to assess two dimensional echocardiography in the evaluation of patients with this disorder. Two dimensional echocardiography indicated that hypertrophy of the interventricular septum is not uniform from apex to base in all patients but may be greatest in the apical, mid or basal third. In addition, the anterior free wall of the left ventricle was involved in the hypertrophic process in approximately 50 percent of patients. Two dimensional echocardiography documented that the location of systolic anterior motion of the mitral valve in patients with hypertrophic cardiomyopathy is most often at the junction of the mitral valve leaflets and chordae tendineae, although the chordae themselves and even the papillary muscles may be involved in this movement. The heterogeneity of these characteristics may enable patients with hypertrophic cardiomyopathy to be classified into subsets of patients in whom meaningful therapeutic and prognostic implications may be derived. Finally, data derived from two dimensional echocardiography have shown that, although the left ventricle in hypertrophic cardiomyopathy conforms in some degree to the configuration of a catenoid, this geometric conformation is unlikely to account for the genesis of this disorder.

When a patient presents with the classic findings of left ventricular failure in the absence of evidence of congenital heart disease or hypertension or without abnormalities indicative of disease involving the coronary arteries, heart valves or pericardium, a presumptive diagnosis of cardiomyopathy is often made. Although in the past the diagnosis of cardiomyopathy was frequently based solely on the exclusion of other diseases,[1] the increasing availability of sophisticated noninvasive diagnostic modalities and cardiac catheterization has enabled the recognition of those patients in whom cardiomyopathy is obscured by findings indicative of other cardiac disorders or in whom cardiomyopathy plays the dominant role when found simultaneously with another form of heart disease.[2–4] Accordingly, the newer diagnostic techniques have made it apparent that patients with cardiomyopathy constitute a greater proportion of patients with cardiac disease than was previously recognized.

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Several factors have coincided to make a systematic approach to the diagnosis of cardiomyopathy of the utmost importance. In addition to the greater clinical recognition of cardiomyopathy, an increasingly long list of causes has been associated with primary myocardial disease, and the differential diagnosis has become both lengthy and involved with several relatively exotic systemic disorders.[5] Further, cardiac muscle can exhibit only a limited variety of responses to the injuries imposed on it by a large number of different disease states. Finally, the diagnosis of cardiomyopathy has been complicated by the fact that no definite etiology can be established in the majority of patients with this disease state.[1] Accordingly, numerous attempts have been made to develop a classification of primary myocardial diseases that would be of diagnostic value with regard to the varying prognostic and therapeutic implications of the individual etiologic entities under consideration.

Some authorities prefer to restrict the designation of primary myocardial disease to those situations in which no cause for cardiac disease can be established.[6] Most authorities include systemic disorders whose cardiac effects predominantly involve the myocardium under the designation of cardiomyopathy,[1,5] because such inclusion serves to establish an awareness of and to provide for an approach to the diagnosis of those systemic disorders whose initial clinical presentation may primarily be manifested by the cardiovascular system. This formulation appears even more preferable at the present time because patients with primary myocardial disease are often detected at an earlier, even asymptomatic, stage of their disease by an abnormal electrocardiogram or findings of an enlarged heart on chest X-ray film or abnormal cardiac findings during a routine physical examination.

Clinical Classification of Cardiomyopathy

Attempts have been made to classify myocardial disease according to clinical, hemodynamic and pathologic features. However, most workers have adopted the classification of the cardiomyopathies initially proposed by Goodwin,[7] which incorporates both pathologic and hemodynamic elements. Goodwin divided all primary myocardial diseases into one of three types: congestive, hypertrophic or restrictive. This classification has proved most useful through the years, and has been especially helpful in providing a basis for the approach to the differential diagnosis of the problem of cardiomyopathy.

Congestive cardiomyopathy consists of a marked destruction of ventricular myocardium that results morphologically in a severely dilated left ventricle with normal or near normal left ventricular wall thickness. From a hemodynamic standpoint, congestive cardiomyopathy is characterized by severe impairment of ventricular contraction manifested by marked generalized ventricular hypokinesia. In contrast, hypertrophic cardiomyopathy presents as a thick-walled left ventricular chamber particularly involving the septum, with normal or near normal cavity size and contractile performance. Whereas the primary hemodynamic abnormality of congestive cardiomyopathy involves diminished left ventricular emptying, the primary abnormality in hypertrophic cardiomyopathy consists of impaired left ventricular filling frequently accompanied by an obstruction to left ventricular outflow. Restrictive cardiomyopathy represents a hybrid of the previous two pathophysiologic types. Thus, the morphologic picture of a restrictive process consists of a left ventricle with a concentric increase in wall thickness and normal cavity size. Hemodynamically, the ventricle in restrictive cardiomyopathy exhibits an impairment of left ventricular filling that may be combined with a reduction of left ventricular emptying secondary to decreased contractile performance.

TABLE I

Echocardiographic Findings in Three Types of Cardiomyopathy

	Congestive	Hypertrophic	Restrictive
LV cavity	++	− or N	N
LV wall thickness	N	+	+
LV contractility	−	+ or N	N or −

LV = left ventricular; − = decreased; N = normal; + = increased.

Classification of Cardiomyopathy by M Mode Echocardiography

The foregoing classification has provided an excellent pathoanatomic basis on which to approach the classification and differential diagnosis of cardiomyopathies by means of M mode echocardiography. Accordingly, patients with cardiomyopathy can readily be identified and classified by means of attention to three ultrasonic measurements of the left ventricle: cavity dimension, left ventricular wall thickness and shortening fraction (minor axis dimensional shortening calculated as LVED − (LVSD/LVED), where LVED and LVSD represent left ventricular end-diastolic and end-systolic-dimensions, respectively) (Table I). In this schema, patients with congestive cardiomyopathy will invariably manifest greatly increased left ventricular cavity size, normal or near normal interventricular septal and posterior wall thicknesses, and a diffusely hypokinetic left ventricle resulting in a markedly reduced shortening fraction.[2] In contrast, patients with hypertrophic cardiomyopathy characteristically manifest reduced or normal left ventricular cavity size and a marked increase in left ventricular wall thickness with a septum that is characteristically 1.3 to 1.5 times as great as the posterobasal wall.[8] With regard to contractile performance, although patients with hypertrophic cardiomyopathy may exhibit diminished contraction of the interventricular septum, overall left ventricular contractile pattern is normal or often hyperkinetic resulting in a high normal or increased shortening fraction. An additional diagnostic but nonspecific feature of obstructive hypertrophic cardiomyopathy present in many patients on M mode recordings is motion of the mitral valve leaflets in systole toward or on the interventricular septum to obstruct the left ventricular outflow tract.[9]

Patients with restrictive cardiomyopathy manifest echocardiographic patterns that bear a similarity to both congestive and hypertrophic types.[4,10] Thus, left ventricular cavity dimension is typically normal in patients with restrictive disorders, although the left ventricle may be minimally dilated or even reduced in size if the ventricular myocardium encroaches on the cavity. Similar to patients with hypertrophic cardiomyopathy, patients with restrictive disorders of the myocardium exhibit a marked increase in left ventricular wall thickness; however, the wall thickening characteristically is symmetric in nature, involving the septum and posterior wall to an equivalent extent. Hemodynamically, restrictive disorders may produce little effect on systolic performance or may result in a significant decrease in overall left ventricular contractile function as exhibited by a reduction in shortening fraction on echocardiography. Thereby, patients with primary myocardial diseases can readily be classified into congestive, hypertrophic or restrictive categories with use of a simple M mode echocardiogram.

M mode echocardiography may also be of value in distinguishing patients with severe left ventricular dysfunction due to congestive cardiomyopathy from those with diminished performance secondary to coronary artery disease.[11]

Etiologic classification: The ability to classify a patient into the category of congestive, hypertrophic or restrictive cardiomyopathy is of substantial aid in identifying the exact cause of the myocardial process.[1] Because disease states associated with primary myocardial involvement characteristically result in a specific category of cardiomyopathy, knowing the nature of the process in an individual patient can enable one to restrict substantially the number of potential etiologic diagnoses. Thus, in patients with congestive cardiomyopathy one should evaluate the possibility of infectious causes, inflammatory processes such as collagen vascular disorders, toxins such as alcohol or cobalt, generalized skeletal muscle disorders such as muscular dystrophy or myocardial processes associated with pregnancy. The vast majority of patients with cardiomyopathy in whom no cause can be identified will be classified into the category of congestive cardiomyopathy. Conversely, hypertrophic cardiomyopathy has not been associated with specific disease entities but rather has most often been shown to be genetic in origin, being transmitted in most patients as an autosomal dominant trait. The cardiac findings observed in hypertrophic cardiomyopathy may also be produced by hypertension or aortic valve disease; however, most authorities prefer to consider such cases under the designation of a primary cardiovascular abnormality. Finally, restrictive cardiomyopathy is most often caused by diseases such as amyloidosis, hemochromatosis and glycogen storage diseases that result in infiltration of the myocardium by foreign substances. So-called obliterative cardiomyopathy, such as that secondary to endocardial fibroelastosis, typically presents in the manner of a restrictive process.

Two Dimensional Echocardiography in Congestive and Restrictive Cardiomyopathy

Several years' experience has demonstrated M mode echocardiography to be an effective tool in the recognition and categorization of primary myocardial disease. The recent availability of two dimensional echocardiography has promised to increase the potential of ultrasound in the diagnosis and management of patients with cardiomyopathy. Two dimensional techniques have already provided important insights regarding the pathophysiology and diagnosis of hypertrophic cardiomyopathy.[12–15] However, overall, the contributions of two dimensional echocardiography to the evaluation of patients with congestive or restrictive cardiomyopathy have been limited to certain specific situations.

Congestive cardiomyopathy: We have performed two dimensional echocardiograms in 40 patients in whom the diagnosis of congestive cardiomyopathy was established by cardiac catheterization or autopsy. Diffuse left ventricular dilation and hypokinesia were observed in all patients with congestive cardiomyopathy and were typically so marked and so generalized that two dimensional echocardiography was rarely required in addition to the M mode technique to diagnose this disorder (Fig. 1). However, two dimensional echocardiography, by virtue of its ability to visualize a greater area of left ventricular myocardium, has provided documentation of segmental asynergy in some patients with coronary artery disease in whom M mode echocardiography was unable to detect segmental dyskinesia. Thus, use of two dimensional techniques alone has enabled the diagnosis of ischemic heart disease to be established in these patients with severe cardiac dysfunction. Two dimensional echocardiography has also proved of value in the recognition of left ventricular mural thrombi that frequently complicate congestive cardiomyopathy (Fig. 2). These mural thrombi, which occasionally occupy substantial areas of the apex of the left ventricular cavity, can rarely be identified solely with M mode techniques.

Restrictive cardiomyopathy: This cardiomyopathy is also a process that results in generalized left ventricular involvement. Accordingly, two dimensional echocardiography rarely adds significantly to the M mode diagnosis of restrictive disorders. At present, two dimensional echocardiography has found its greatest utility in the evaluation of restrictive cardiomyopathy in regard to the differentiation from hypertrophic cardiomyopathy, and in the demonstration of right ventricular and biatrial involvement in infiltrative processes such as amyloidosis.[16]

Two Dimensional Echocardiography in Hypertrophic Cardiomyopathy

Two dimensional echocardiography has made its most significant contributions in the evaluation of patients with hypertrophic cardiomyopathy (patients with features of this disorder have also been considered under the designations idiopathic hypertrophic sub-

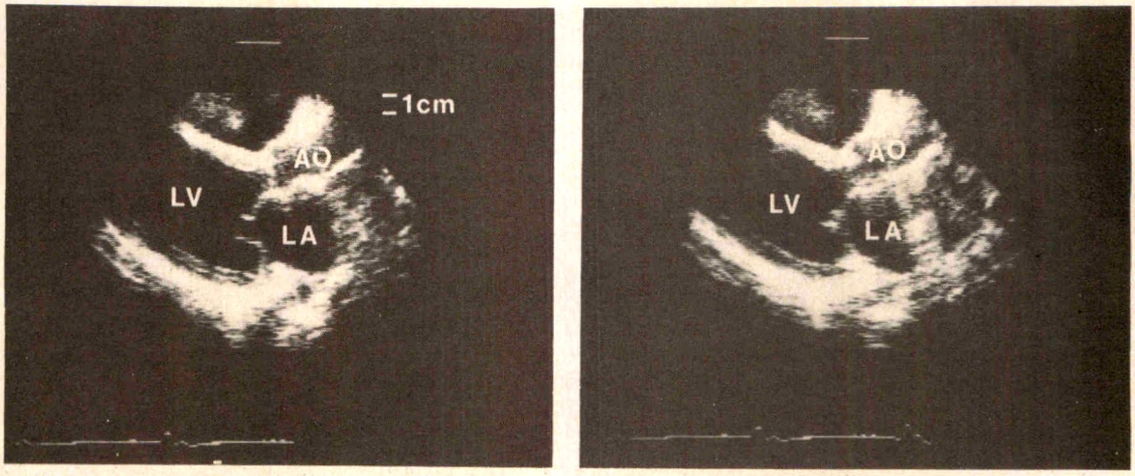


FIGURE 1. End-diastolic (**left**) and end-systolic (**right**) long axis two dimensional echocardiograms obtained in a patient with congestive cardiomyopathy. A dilated left ventricle (LV) with diffuse hypokinesia is observed. AO = aorta; LA = left atrium.

aortic stenosis, asymmetric septal hypertrophy, hypertrophic obstructive cardiomyopathy and other disorders[17]). Although a constellation of abnormalities on M mode echocardiography has been reported in hypertrophic cardiomyopathy including asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, anterior displacement of the mitral C point, mid systolic closure of the aortic valve leaflets and hypokinetic septal contraction, none of these findings have been found to have perfect sensitivity or specificity for this disorder. Moreover, M mode echocardiography has provided few data regarding several controversial aspects of hypertrophic cardiomyopathy, including the precise site of systolic anterior motion and the geometric changes of the left ventricle associated with this disorder.

Technical Advantages

The greater field of view and spatial orientation afforded by two dimensional echocardiography have often

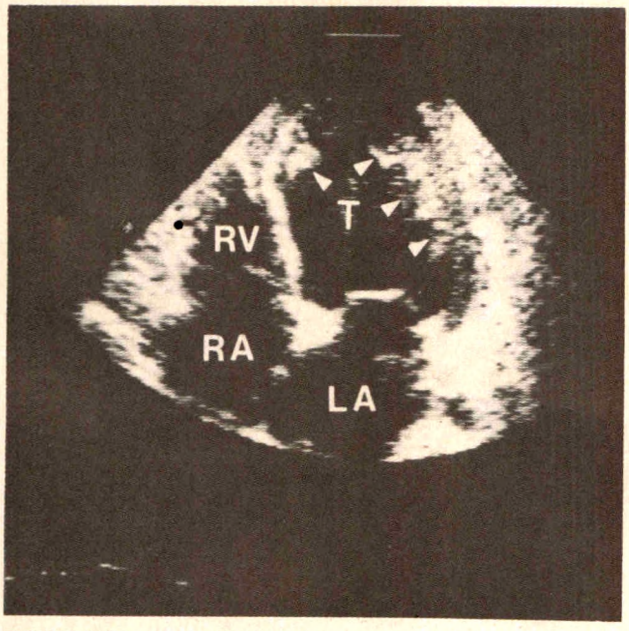


FIGURE 2. Truncated apical four chamber view of the two dimensional echocardiogram of a patient with congestive cardiomyopathy and mural thrombus (**T, arrows**). RA = right atrium; RV = right ventricle.

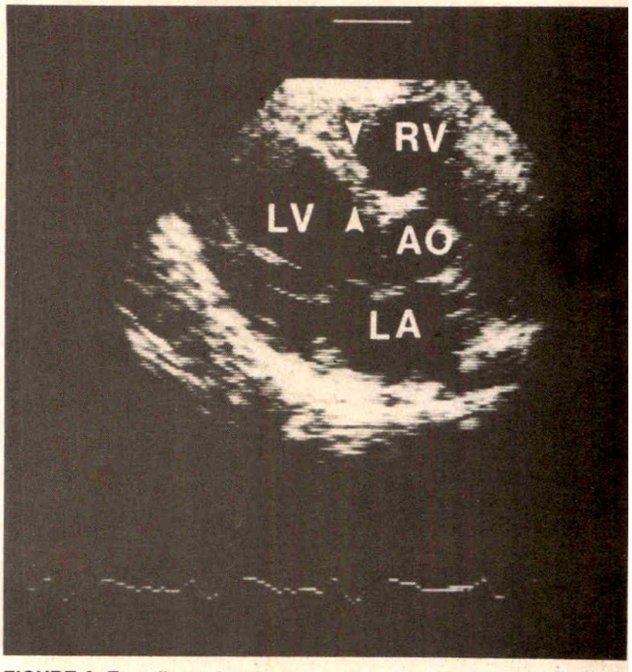


FIGURE 3. Two dimensional echocardiogram in a long axis plane of a patient whose interventricular septum exhibits a marked anterior angulation. An M mode beam could traverse the septum tangentially through the path depicted by the **arrows** so as to give the false appearance of asymmetric septal hypertrophy in this patient. Abbreviations as before.

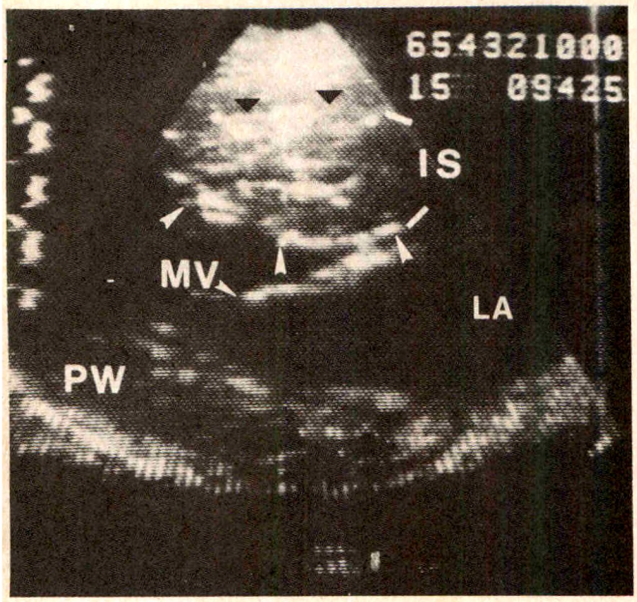


FIGURE 4. Long axis two dimensional echocardiogram of a patient with hypertrophic cardiomyopathy whose interventricular septum (IS) is thickest at the level of the tips of the mitral valve (MV) leaflets. PW = posterior wall.

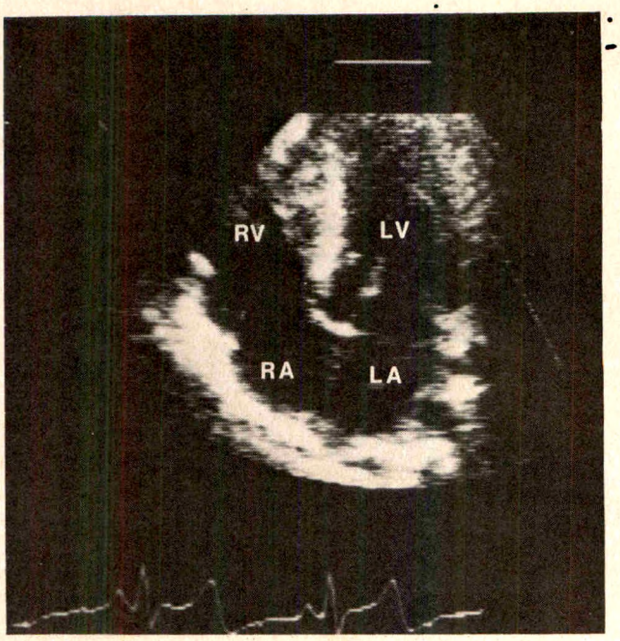


FIGURE 5. Apical four chamber two dimensional echocardiogram in a patient with hypertrophic cardiomyopathy in whom the interventricular septum manifested its greatest width in the apical one third.

enabled this technique to provide clarification regarding the diagnosis of hypertrophic cardiomyopathy in patients with an equivocal M mode echocardiogram. Thus, impediments to ultrasonic transmission may often render M mode echocardiograms of high quality difficult to obtain from the left parasternal area, especially in regard to definition of the right and left ventricular surfaces of the septum. In such patients technically adequate two dimensional echocardiograms may be obtained from the apex at the point of maximal cardiac impulse and provide definitive diagnostic information regarding the presence of asymmetric septal hypertrophy. An additional technical consideration relates to the spurious appearance of disproportionate septal thickening, which may be manifested by M mode echocardiograms in patients with a marked anterior orientation of the septum. Thus, Fowles et al.[18] demonstrated that such anterior orientation may result in the M mode ultrasonic beam's traversing the septum tangentially so as to give a falsely increased appearance of septal thickness (Fig. 3). Two dimensional echocardiography is capable of recognizing such artifacts and can demonstrate the true thickness of the interventricular septum as well as indicate the anterior orientation of the septum responsible for the M mode echocardiographic findings.[18]

Of greater importance than these technical advantages is the potential that two-dimensional imaging offers in providing valuable insights into many of the unresolved questions concerning hypertrophic cardiomyopathy. Thus, two dimensional echocardiographic observations have been reported in regard to the uniformity of myocardial hypertrophy, the site of systolic anterior motion of the mitral valve and the position of the papillary muscles within the left ventricular cavity in patients with this disorder.[12–15,19–22] Recently, we analyzed the cross-sectional echocardiograms of 25 patients with hypertrophic cardiomyopathy. The diagnosis of hypertrophic cardiomyopathy was reached when (1) no other cardiac abnormality could account for the findings, (2) a hypertrophied and nondilated left ventricle with or without a dynamic intraventricular obstruction was demonstrated at cardiac catheterization, or (3) the classic features of this disorder were present on physical examination and M mode echocardiography.[3,8,9,12] In addition to the aforementioned issues, we have addressed ourselves to the hypothesis that a catenoid shape of the interventricular septum played an important role in the genesis of hypertrophic cardiomyopathy.[23]

Uniformity of Asymmetric Septal Hypertrophy

One of the most consistent M mode echocardiographic findings recorded in patients with hypertrophic cardiomyopathy was asymmetric septal hypertrophy or a disproportionate thickening of the interventricular septum 1.3 to 1.5 times greater than the left ventricular posterior wall.[8,24] However, some patients were observed in whom left ventricular hypertrophy was concentric on M mode echocardiography.[25] Furthermore, studies utilizing biventricular cineangiography indicated that the interventricular septum was not uniformly hypertrophied in its basal to apex length, but was often thicker in its mid portion than at either extreme.[26,27] Because two dimensional echocardiography enables visualization of nearly the entire interventric-

ular septum, preliminary studies were undertaken to determine the pattern of septal hypertrophy in patients with hypertrophic cardiomyopathy.[19]

Long axis view of septal hypertrophy: Two dimensional echocardiograms were reviewed in every patient in each of the three standard orthogonal planes: long axis, short axis and four chamber view. For purposes of analysis, the septum was divided into thirds in apex to base length. The results showed that in the long axis view the septum was hypertrophied both absolutely and with respect to the posterobasal wall in each of the 25 patients; however, the pattern of hypertrophy from base to apex varied within the group of patients studied. The majority of patients (69 percent) exhibited a gradual increase in septal thickness that began at the base, reached its greatest extent in the middle third in an area just at or below the tips of the mitral leaflets, and tapered gradually toward the apex (Fig. 4). In 26 percent of patients the septum appeared to be hypertrophied in a uniform fashion in the long axis view, with septal thickness being equivalent in the middle and basal thirds, in one patient (4 percent) the septum appeared of greatest thickness in the basal third.

Apical four chamber view: Although the apical portion of the septum was frequently not recorded in the long axis, the apical four chamber view visualized this structure throughout its apex to base length in each patient. The appearance of the septum in the four chamber view agreed with that observed in the long axis projection in all but two patients. In both patients the septum appeared to be of uniform shape in the long axis view, but in one patient it clearly exhibited greater hypertrophy in the middle third in another the greatest thickness in its apical third in the four chamber projection (Fig. 5).

Short axis view: This view provided the opportunity to evaluate the thickness of the myocardium throughout the circumference of the left ventricle for the first time. For descriptive purposes the interventricular septum was divided into anterolateral and posteromedial halves. The remainder of the left ventricle was again bisected into a posteroinferior region and a free wall. Of 19 patients in whom left ventricular wall thickness could be discerned throughout the circumference of the left ventricle in an area of mid septum at or just below the tips of the mitral leaflets, all exhibited hypertrophy of the anterolateral septum. Equivalent hypertrophy of the posteromedial septum was observed in 15 patients, although this segment manifested a slightly greater degree of hypertrophy than the anterolateral septum in two patients (11 percent) and no hypertrophy in another two. The free wall of the left ventricle was observed to share in the hypertrophic process in 10 of 19 patients (53 percent) (Fig. 6) and was hypertrophied to an equivalent extent as the interventricular septum in 11 percent. Hypertrophy of some aspect of the posteroinferior left ventricular wall was observed in only 3 (16 percent) of 19 patients, and was lesser in magnitude than the septal hypertrophy in every patient except the one whose septum appeared to be hypertrophied to the greatest extent in the apical third in the long axis projection.

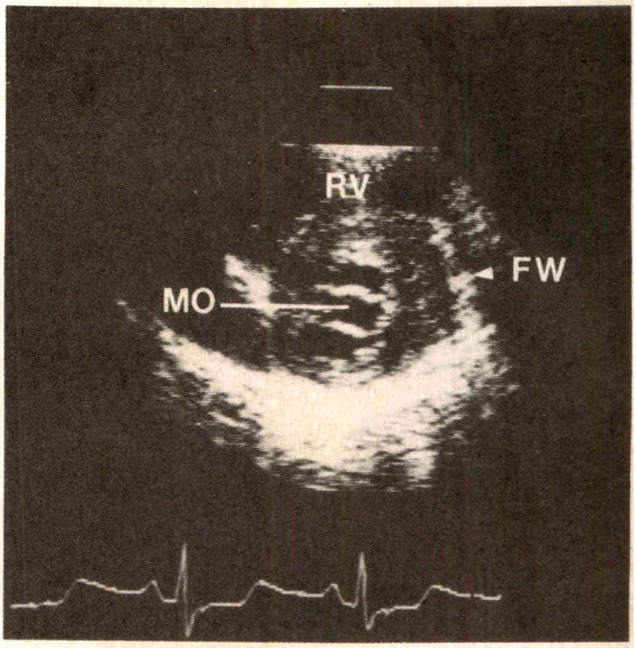


FIGURE 6. Short axis two dimensional echocardiogram of a patient with hypertrophic cardiomyopathy with hypertrophy of the anterior free wall (FW) of the left ventricle as well as of the interventricular septum. MO = mitral valve orifice.

Patterns of ventricular hypertrophy: On the basis of the foregoing observations, it appears that there is a great heterogeneity in the pattern of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. Thus, the hypertrophic process was observed to involve the anterior free wall of the left ventricle in addition to the interventricular septum in more than half of the patients studied, a finding similar to that initially observed by Teare.[28] Furthermore, the distribution of hypertrophy within the interventricular septum does not occur in a uniform pattern in this disorder. This hypertrophy is greatest in the anterolateral and middle third portions of the septum in the short and long axes, respectively, in the majority of patients, but equivalent or even greater in extent in other areas of the septum in a significant minority of patients. Although the hemodynamic, prognostic and therapeutic implications of these various patterns of myocardial hypertrophy cannot be resolved in this limited group of patients, they remain an important area for future investigation and promise to increase further the role of two dimensional echocardiography in the evaluation of patients with hypertrophic cardiomyopathy.

Location of Systolic Anterior Motion

One of the initial observations made by M mode echocardiography in patients with hypertrophic cardiomyopathy was the encroachment on the left ven-

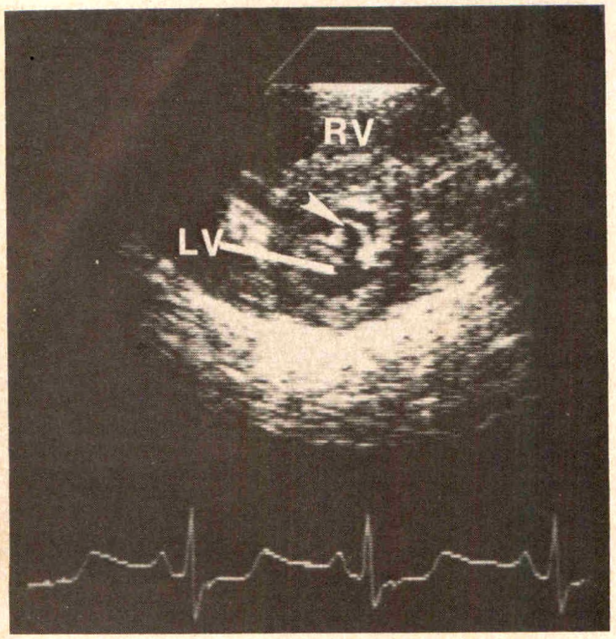


FIGURE 7. Short axis two dimensional echocardiogram obtained in mid systole in a patient with hypertrophic cardiomyopathy. The anterior mitral leaflet (arrow) can be seen arching anterior and clearly playing a major role in systolic anterior motion.

tricular outflow tract during systole by a group of echoes associated with the mitral valve leaflets.[9] These echoes were believed to represent systolic anterior motion of the mitral valve leaflets and were immediately implicated in the genesis of the intraventricular obstruction frequently associated with this cardiac disorder. Although considerable controversy focused on whether systolic anterior motion of the mitral valve was the result of tensing of the chordae tendineae due to abnormal papillary muscle location[27] or was secondary to suction exerted by a Venturi effect,[12] little question was raised that these echoes actually represented movement of the mitral valve leaflets. However, the advent of two dimensional echocardiography brought into question the exact structures involved. Several investigators[13,14] interpreted the two dimensional echocardiograms as demonstrating systolic motion of the papillary muscles or chordae tendineae rather than of mitral leaflets.

Thus, as was true for the pattern of ventricular hypertrophy in patients with hypertrophic cardiomyopathy, the site of anterior motion also appears to be heterogeneous. In the majority of cases long and short axis and four chamber two dimensional echocardiograms clearly indicate that systolic anterior motion involves the tips of the mitral valve leaflets at the junction of the chordae tendineae as identified by the point of coaptation of mitral valve leaflets (Fig. 7). In most cases systolic anterior motion also involved the chordae tendineae themselves, and in only a small minority of cases does the systolic anterior motion appear to involve the chordae tendineae exclusively. Although systolic anterior motion of the papillary muscles and of the entire length of the anterior mitral leaflet was also observed in a subset of patients, these findings always occurred in conjunction with systolic anterior motion involving the chordae tendineae or mitral leaflet tips and seem to correlate with the existence of significant obstruction to the left ventricular outflow tract. In only one case in this study was the existence of the mid ventricular obstruction able to be documented.

Mechanism of interventricular obstruction: The acute angle anterior bend formed by the tips of the mitral valve leaflets does not lend support to the theory that systolic anterior motion is a result of tensing of the chordae tendineae due to the displacement of the papillary muscles by the hypertrophied interventricular septum. However, an almost invariable occurrence in the presence of a significant intraventricular gradient was a markedly reduced left ventricular outflow tract throughout diastole with most of the length of the anterior mitral valve leaflet positioned on the interventricular septum. The most reasonable interpretation of these data would seem to be that intraventricular obstruction is related to malposition of the papillary muscles resulting in anterior displacement of the mitral apparatus that decreases the size of the left ventricular outflow tract and on which is superimposed a marked tethering at the tips of the mitral valve leaflets.

Evaluation of Left Ventricular Geometry

A variety of changes in left ventricular geometry have been reported with angiographic studies in patients with hypertrophic cardiomyopathy.[26,27] Thus, prominent and displaced papillary muscles as well as an orientation of the long axis of the left ventricle toward the left atrium rather than the aorta have been observed in patients with this cardiac disorder. Two dimensional echocardiography provides a unique opportunity to evaluate intracavitary left ventricular anatomy through multiple planes. Therefore, we analyzed the cross-sectional echocardiograms performed in this group of patients in regard to possible alterations of left ventricular geometry.

Role of the papillary muscles: As with previous aspects of hypertrophic cardiomyopathy, patients in this study did not have uniform findings in regard to left ventricular anatomy. The hypertrophied interventricular septum encroached on the left ventricular outflow tract so that the left ventricle in diastole was oriented to the left atrium rather than the aorta in both long axis and short axis and four chamber apical views in all but two of our patients. The position of the papillary muscles were evaluated in short axis view. Compared with normal subjects whose papillary muscles are typically recognized as discrete structures in the posterior half of the left ventricular cavity, our patients had as the characteristic finding prominent papillary muscles that were located in the center (63 percent) or even in the anterior half (10 percent) of the left ventricle. The orientation of the papillary muscles with respect to each other remained unchanged from the normal patients with hypertrophic cardiomyopathy. Thus, these data

indicate that in most patients with hypertrophic cardiomyopathy the left ventricle is characterized by a prominent septal bulge and anteriorly located papillary muscles that result in an orientation of the left ventricle toward the left atrium rather than the aorta.

Findings After Septal Myectomy

Although we have not accumulated any experience with two dimensional echocardiography after septal myectomy in the treatment of hypertrophic cardiomyopathy, Fowles et al.[18] have reported preliminary findings in two patients treated in this manner. In each patient evaluated in that study, surgical therapy was followed by the appearance on two dimensional echocardiography of thinning of the interventricular septum as well as disappearance of previously recognized systolic anterior motion of the mitral valve. Further alterations in papillary muscle position and chamber orientation were not recorded. It is likely that two dimensional echocardiography will provide a most useful method not only to assess the efficacy of myectomy in the surgical therapy of hypertrophic cardiomyopathy but also to evaluate the mechanisms by which this procedure corrects the hemodynamic dysfunction.

Conclusion

Echocardiography has assumed an important position in the identification and differential diagnosis of primary myocardial disease. Two dimensional echocardiography has amplified the role of ultrasound in the evaluation of patients with cardiomyopathy in specific areas, and has been of particular value in the setting of hypertrophic cardiomyopathy. It is anticipated that further experience in observing the response to therapy and the natural history of patients with cardiomyopathy who manifest specific findings on two dimensional echocardiography will result in an even greater role for this technique in this patient population in the future.

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Value of Radionuclide Imaging Techniques in Assessing Cardiomyopathy

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Radionuclide imaging techniques add an important dimension to the diagnosis, classification and management of myocardial disease. The gated blood pool scan provides information allowing determination of the functional type of cardiomyopathy (congestive, restrictive or hypertrophic) as well as evaluation of ventricular performance. Myocardial perfusion imaging with thallium-201 is useful in distinguishing congestive cardiomyopathy from severe coronary artery disease and also in depicting septal abnormalities in hypertrophic cardiomyopathy. Radionuclide techniques also prove useful in following progression of disease and in evaluating the efficacy of therapeutic interventions.

The term cardiomyopathy refers to disease of the heart muscle. In clinical practice cardiomyopathies demonstrate a defect in the function of the myocardium precluding the heart from maintaining adequate systemic perfusion with normal filling pressures. The cardiomyopathies are traditionally grouped into categories reflecting function[1] or etiology[2] (Table I). For the purpose of this discussion, the former classification, including congestive (or dilated), restrictive and hypertrophic cardiomyopathy will be used. The differentiation of the various classifications has diagnostic, therapeutic and prognostic implications, yet may be difficult to determine clinically.

Radionuclide imaging techniques can assist in this differentiation, quantify the severity of diminished myocardial performance and assess therapeutic responses.[3] Gated cardiac blood pool scanning or radionuclide angiography permits evaluation of ejection fraction, ventricular size and wall motion and interventricular septal thickness and configuration.[4] With this information, the functional class of the cardiomyopathy can be established (congestive, restrictive or hypertrophic), and various etiologic possibilities are suggested. Nonmyocardial forms of heart disease that secondarily involve the myocardium can simulate a primary cardiomyopathy. The diagnosis can frequently be clarified with radionuclide techniques. Myocardial imaging with thallium-201 is useful in detecting disease that replaces (for example, fibrosis) or displaces (for example, metastatic neoplasm) myocardium. It is of particular value in differentiating myocardial dysfunction resulting from coronary artery disease from congestive cardiomyopathy and in depicting septal abnormalities in hypertrophic cardiomyopathy. The use of radionuclide techniques, together with other noninvasive approaches, such as ultrasound, adds an important dimension in the diagnosis and management of patients with cardiomyopathy. In this review, the radionuclide findings in the three functional types of cardiomyopathy will be discussed.

Congestive Cardiomyopathy

The most common of the cardiomyopathies, congestive (or dilated) cardiomyopathy, is characterized by evidence of left- and right-sided heart failure. Although the clinical course of the disease may be quite variable,[5] the ventricles are invariably dilated, often hypertrophied and

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TABLE I

Classification of the Common Cardiomyopathies

Etiology	Congestive (Dilated)	Restrictive	Hypertrophic
Idiopathic	Idiopathic	Endocardial fibroelastosis (restrictive type)	Obstructive
	Postpartum		
	Endocardial fibroelastosis (dilated type)	Endomyocardial fibrosis	Nonobstructive
		Davies' disease	
		Loeffler's disease	
Toxic	Ethanol		
	Heavy metals (cobalt, etc.)		
	Doxorubicin		
Inflammatory	Infective		
	Viral		
	Diphtheria		
	Chagas' disease		
	Noninfective		
	Rheumatic myocarditis	Scleroderma	
	Systemic lupus erythematosus	Amyloid	
	Sarcoidosis	Neoplasm	
	Polyarteritis		
Metabolic	Thiamine deficiency	Hemochromatosis	
	Acromegaly	Glycogen storage disease	
	Thalassemia		
Neuromuscular	Friedrich's ataxia		
	Muscular dystrophy		

commonly have mural thrombi.[6] The stroke volume is diminished and the heart rate may be increased, usually with reduced cardiac output. The chest X-ray film demonstrates generalized cardiomegaly.

Radionuclide angiography: The gated blood pool scans of patients with congestive cardiomyopathy have a typical appearance. Both ventricles are dilated and have diminished wall motion. Usually the left ventricle is affected more than the right. The left ventricular ejection fraction is usually less than 0.3 and occasionally as low as 0.1. The atria and pulmonary artery may be dilated. An example of a gated blood pool scan from a patient with congestive cardiomyopathy is shown in Figure 1. Patients with severe coronary artery disease and repeated myocardial infarction may have gated blood pool scans resembling those of congestive cardiomyopathy. In general, a global or homogeneous reduction in wall motion occurs in congestive cardiomyopathy,[7] whereas the basal septum and anterobasal segment often move normally in severe coronary disease. Nevertheless, the distinction between congestive cardiomyopathy due to coronary disease and primary congestive cardiomyopathy may be difficult. Some patients with left heart failure due to a left ventricular aneurysm may also have gated blood pool scans resembling those of congestive cardiomyopathy.[8] Although the gated blood pool scan usually identifies the presence of an aneurysm, in some patients the scan may be misleading. Thallium perfusion imaging is often useful in this situation, but cardiac catheterization and left ventriculography may be required to distinguish definitively between these disorders.

Myocardial imaging with thallium: Myocardial perfusion imaging at rest with thallium-201 in patients with congestive cardiomyopathy demonstrates ventricular dilatation with either normal or diffuse homogenous reduction in uptake (Fig. 2). Congestive heart failure due to severe or repeated myocardial infarction, or both, can often be distinguished from congestive cardiomyopathy using thallium-201 scintigraphy. It is for this purpose that thallium-201 is most useful in suspected congestive cardiomyopathy. As shown by Bulkley et al.,[7] congestive heart failure due to coronary disease is usually associated with large (more than 40 percent) circumferential defects in the thallium-201 image in any single projection (Fig. 3). Although some patients with congestive cardiomyopathy may have thallium-201 defects, those defects are almost always less than 20 percent in circumference. Although the thallium perfusion findings may not be totally specific, they can help determine whether congestive cardiomyopathy is primary or due to coronary artery disease.

Comparison with echocardiography: Cardiac ultrasound is also useful in evaluating ventricular size and function in congestive cardiomyopathy. However, as pointed out by Corya et al.,[9] it may be difficult to distinguish congestive cardiomyopathy from severe coronary disease with one dimensional echocardiography. Two dimensional echocardiography appears to offer significant advantages over the one dimensional approach. Folland et al.,[10] showed that ejection fraction obtained using two dimensional echocardiography correlates reasonably well with that obtained by cine and radionuclide techniques. Furthermore, segmental wall motion abnormalities may be detected using cross-sectional ultrasound.[11] The problem of adequate penetration of the ultrasonic beam in certain patients with lung disease or an abnormal chest configuration may make the technique difficult or impossible. However, radionuclide images can be obtained in all patients and in multiple oblique projections.

Serial examinations of the heart using radionuclide techniques may allow evaluation of progression of disease or efficacy of therapeutic interventions. For example, radionuclide angiocardiography has been used

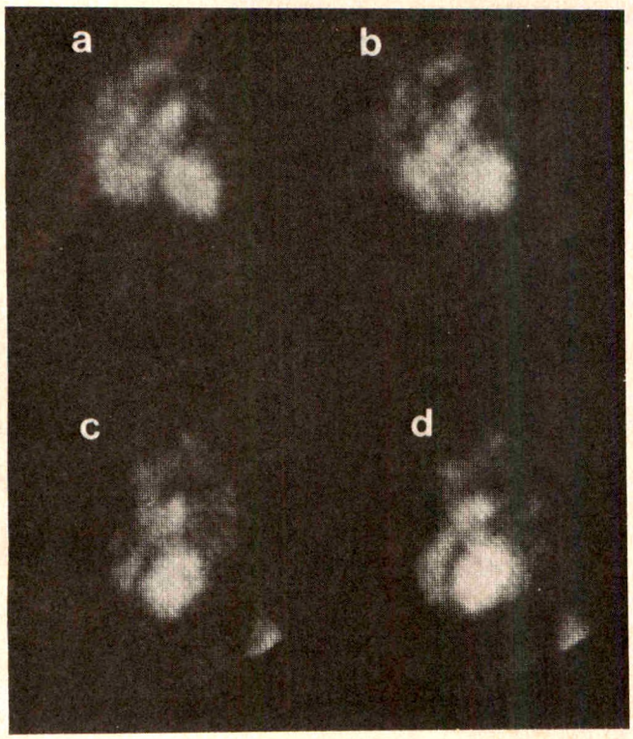


FIGURE 1. Anterior (**upper**) and 50° left anterior oblique (**lower**) views at end-systole (**left**) and end-diastole (**right**) of the gated blood pool scan of a patient with congestive cardiomyopathy. Note the generalized cardiomegaly and the marked reduction of left ventricular contraction. a = anterior end-systolic frame; b = anterior end-diastolic frame; c = LAO end-systolic frame; d = LAO end-diastolic frame.

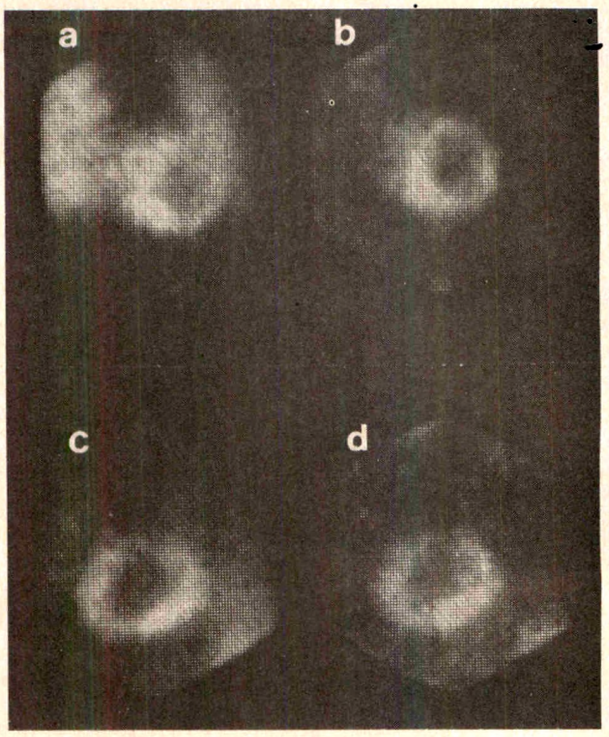


FIGURE 2. Anterior (**upper**) and left anterior oblique (**lower**) projections of the exercise (**left**) and delayed (**right**) thallium-201 perfusion scans of a patient with congestive cardiomyopathy (the same patient as in Fig. 1). There is thallium uptake throughout the myocardium, despite the severe wall motion abnormalities. Note the increased pulmonary thallium activity during exercise and the increase in left ventricular size during exercise. a = anterior exercise image; b = anterior delayed image; c = LAO exercise image; d = LAO delayed image.

to assess doxorubicin cardiotoxicity serially.[12] In addition, comparison of the gated blood pool scans at rest and during exercise may allow detection of early and subtle left ventricular dysfunction when the scan at rest is normal.[13]

Restrictive Cardiomyopathy

Restrictive cardiomyopathy is a rare disease in the United States and represents the least common group of cardiomyopathy. This form of cardiomyopathy causes signs of right- and left-sided heart failure with a normal-sized heart and may mimic constrictive pericarditis. Neck vein distension with rapid *x* and *y* descents, and pulsus paradoxus may be present. Pathologically, the disease is characterized by either an infiltrative process or endocardial fibrosis. Physiologically, the hallmark of restrictive cardiomyopathy is low ventricular compliance, resulting in inadequate filling, even in the presence of high atrial pressures.

The gated blood pool scan is useful in distinguishing restrictive from congestive cardiomyopathy by visualization of ventricular size. In the congestive form, the chambers are diffusely enlarged, whereas in the restrictive form, ventricular size is normal. Ventricular wall motion may be mildly depressed or, in the early stages of the disease, may be normal.

Differentiation of restrictive cardiomyopathy from constrictive pericarditis: Clinically this differentiation may be very difficult. Infiltrative cardiomyopathy is often associated with increased ventricular wall thickness, and myocardial imaging with thallium-201 may be helpful. Increased wall thickness may also be detectable with ultrasound.[14] Ultrasound may also permit detection of diastolic posterior wall flatness, a finding that Voelkel et al.[15] believe characteristic of

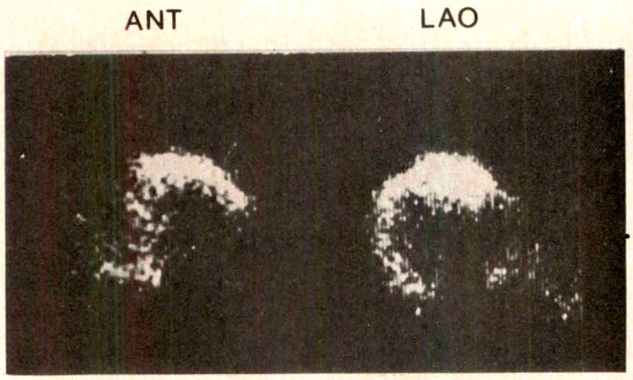


FIGURE 3. Anterior (ANT) and left anterior oblique (LAO) projections of the rest thallium-201 scan of a patient with severe coronary artery disease and the clinical presentation of congestive cardiomyopathy. Note the large inferoposteroapical thallium perfusion defect.

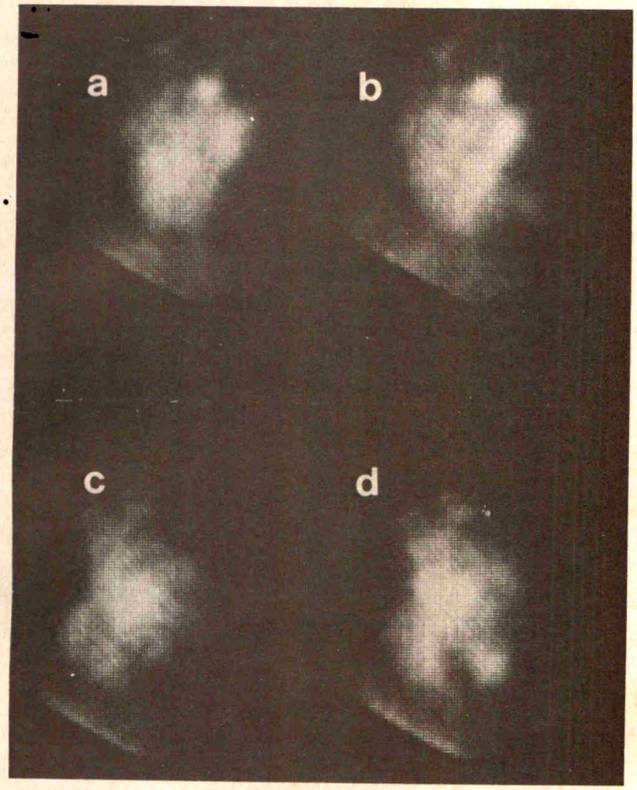


FIGURE 4. Anterior (**upper**) and 50° left anterior oblique (**lower**) views of the gated blood pool scan of a patient with hypertrophic cardiomyopathy. Note the disproportionate upper septal thickening in the left anterior oblique end-diastolic frame (d). Note also the loss of the normal septal concavity toward the left ventricle and the near cavity obliteration at end-systole. a = anterior end-systolic frame; b = anterior end-diastolic frame; c = left anterior oblique end-systolic frame; d = left anterior oblique end-diastolic frame.

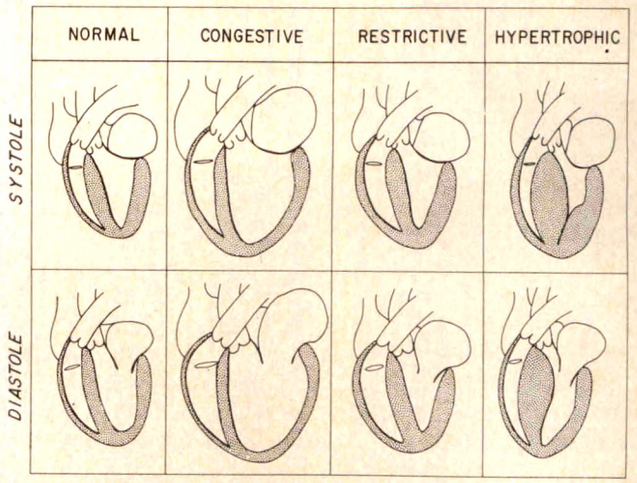


FIGURE 5. Illustration of the 50° left anterior oblique views of the heart in the different types of cardiomyopathy at end-systole and end-diastole. The radionuclide features of each type are discussed in the text.

pericardial disease. Occasionally, it may be impossible to determine clinically whether the patient has restrictive cardiomyopathy or constrictive pericardial disease. In such a situation right ventricular or pericardial biopsy, or both, may be necessary.

Hypertrophic Cardiomyopathy

Until the use of noninvasive imaging techniques became widespread, reports concerning hypertrophic cardiomyopathy were confusing because different names were used to describe different features of the disease. Idiopathic hypertrophic subaortic stenosis (IHSS) was used by Braunwald et al.[16] to describe the dynamic outflow obstruction in patients with hypertrophic cardiomyopathy,[16] whereas Brent et al.[17] used the term muscular subaortic stenosis. Goodwin et al.[18] used the term hypertrophic obstructive cardiomyopathy (HOCM), emphasizing the myocardial abnormality. Hypertrophic cardiomyopathy is a term that encompasses those hearts with and without outflow obstruction.

Pathologically, the disease is characterized by left ventricular hypertrophy, generally asymmetric, with the septum thickened disproportionately.[19–22] The left ventricular outflow obstruction is caused by the hypertrophic septum and abnormal anterior motion of the anterior leaflet of the mitral valve.[23,24] There may be associated mitral regurgitation. Heart failure is a result of diminished left ventricular compliance, outflow obstruction and mitral regurgitation.

Echocardiography: Cardiac ultrasound has proved very useful in the diagnosis of hypertrophic cardiomyopathy. Asymmetric septal hypertrophy is generally easily detected with echocardiography, but it is not a specific finding and may be caused by right ventricular hypertrophy.[25] Systolic anterior motion of the anterior leaflet of the mitral valve can also be detected with ultrasound and was thought to be diagnostic of hypertrophic cardiomyopathy with obstruction.[26] Several reports have indicated that this finding also is not totally specific.[27–29]

Radionuclide imaging: Radionuclide techniques have been shown to be helpful in the diagnosis of hypertrophic cardiomyopathy. The gated blood pool scan permits visualization of the interventricular septum when obtained in the 40° to 50° left anterior oblique view. Normally, the interventricular septum is curvilinear, concave toward the left ventricle. As shown by Pohost et al.,[30] the gated blood pool scan reveals disproportionate upper septal thickening in approximately 50 percent of patients with hypertrophic cardiomyopathy and loss of normal septal concavity toward the left ventricle in 73 percent (Fig. 4). The latter finding, although more frequent, is less specific, being found in patients with aortic stenosis and in some normal people. In the anterior projection, left ventricular cavity obliteration may occasionally be observed.

Thallium myocardial imaging has been used to assess hypertrophic cardiomyopathy. The scans may demonstrate asymmetric septal hypertrophy.[31] Greater basal septal thickness relative to posterior wall thickness was believed to be an indicator of left ventricular outflow obstruction. As shown by Mews et al.,[32] the gated

thallium-201 scan in patients with hypertrophic cardiomyopathy demonstrated disproportionate upper septal thickening at end-diastole, similar to that observed at end-diastole in the gated blood pool scan.

A summary of the cardial configuration in the various types of cardiomyopathy is shown in Figure 5. The left anterior oblique views illustrate how radionuclide techniques can differentiate among the different functional types.

Summary

Radionuclide techniques are easily obtainable noninvasive examinations that provide useful information in the evaluation, diagnosis and management of patients with cardiomyopathy. The gated blood pool scan allows determination of ventricular size, configuration and wall and septal thickness. These data permit diagnosis of the functional class of the cardiomyopathy (congestive, restrictive or hypertrophic). Thallium-201 perfusion imaging adds further information and is particularly useful in distinguishing congestive cardiomyopathy from severe coronary artery disease and in depicting septal abnormalities in hypertrophic cardiomyopathy.

Useful as these techniques are, they are not substitutes for traditional approaches to diagnosis. Careful history taking and physical examination, as well as scrutiny of the electrocardiogram, chest X-ray film and echocardiogram should be standard practice for evaluation of patients with suspected cardiomyopathy. Judicious use of noninvasive techniques may obviate the need for cardiac catheterization in many patients.

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Two Dimensional Echocardiography in Congenital Heart Disease

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Two dimensional echocardiography has enhanced the ability of the clinician to define accurately intracardiac anatomy and great vessel relations. By visualizing relations of the great arteries and determining ventricular situs in the parasternal short axis planes and by assessing the relation of the great arteries to ventricles, atrioventricular (A-V) valves and the interventricular septum in the parasternal and apical long axis view, complex congenital heart disorders can readily be differentiated. The subcostal approach allows accurate identification and localization of interatrial and interventricular septal defects. Utilizing the apical parasternal four chambered or subcostal four chambered view, complex malformations of the A-V valves such as complete endocardial cushion defect and Ebstein's anomaly can readily be appreciated. The suprasternal approach has allowed direct visualization of a coarcted aortic segment. The differentiation of left and right ventricular outflow obstruction is also possible. In some patients, it is possible to achieve an accurate diagnosis with two dimensional echocardiography alone. In others, two dimensional echocardiography provides accurate and detailed information with regard to spatial anatomy and valve morphology so that invasive studies can be performed more expeditiously, with less contrast agent and hence with greater safety.

With regard to future developments, better resolution capability with newer instrumentation and combined two dimensional echocardiography with Doppler blood flowmeter studies may provide even greater diagnostic accuracy in the evaluation of patients with congenital heart disorders.

The ability of two dimensional echocardiography to visualize spatial relations is particularly useful when evaluating patients with congenital heart disease. A variety of instruments are available for recording two dimensional echocardiograms.[1–4] The echocardiographic approach to congenital heart disorders differs from the clinical approach. Instead of differentiating cyanotic from noncyanotic congenital heart disorders, stressing ventricular dominance, pulmonary blood flow and pulmonary hypertension, two dimensional echocardiography visualizes anatomic relations and the structural defects.

Examination Technique

Several different cross-sectional planes are employed when evaluating patients with congenital heart disease. These consist of a parasternal long axis view, parasternal short axis views and the apical four chambered view. In addition, the subcostal and suprasternal approaches are also routinely employed. Space does not permit detailed description of all these anatomic planes, and there are many excellent publications[5–7] addressing themselves to these various planes. For the purpose of this review, certain planes will be discussed in greater detail.

Subcostal approach (Fig. 1): The subcostal approach is particularly useful in evaluating infants and children with a variety of congenital

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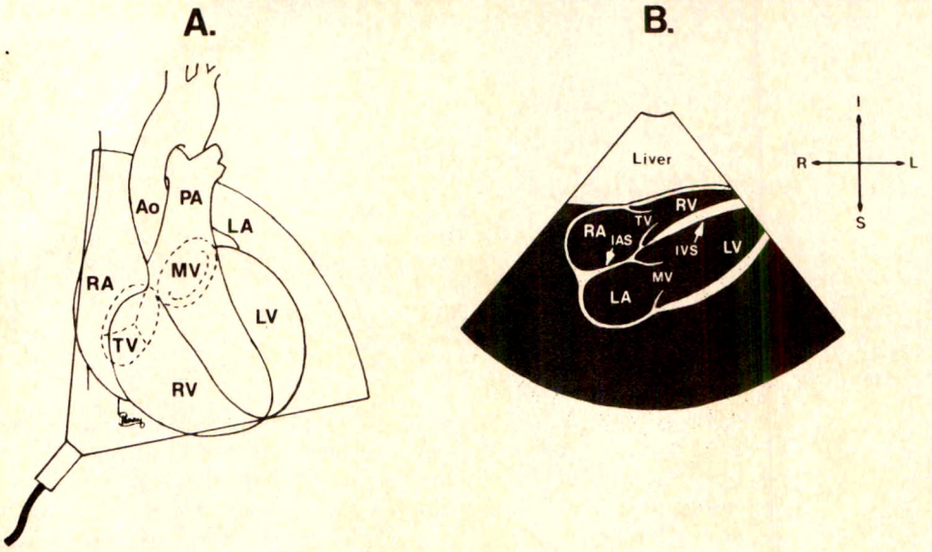


FIGURE 1. Diagrammatic illustration (**B**) obtained from the subcostal approach (**A**). The beam is perpendicular to the interatrial and membranous portion of the interventricular septum (IVS). Right atrium (RA), interatrial septum (IAS) and left atrium (LA) are clearly demonstrated as are the tricuspid (TV) and mitral (MV) valves. The interventricular septum separating the right ventricle (RV) and the left ventricle (LV) is well demonstrated. The liver is normally seen as a dense mass of echoes. Ao = aorta; I = inferior; L = left; PA = pulmonary artery; S = superior.

cardiac disorders.[7,8] One group of investigators[7] utilizing the subcostal approach place the transducer along a coronal plane parallel to a line between the patient's shoulders with the scan plane tilted about 45° downward from the plane of the anterior chest wall. This view allows visualization of both the atrial cavities, the interatrial septum, the ventricular septum, both ventricular cavities and the atrioventricular (A-V) valves. Because both the interatrial septum and membranous portion of the interventricular septum are somewhat perpendicular to the ultrasonic beam, they are usually completely imaged, and very little echo dropout occurs. Other investigators have used a slightly modified approach.[8] Initially, the transducer is placed in the subcostal area, perpendicular to the frontal plane. The echographic beam is oriented parallel to the horizontal axis of the trunk to identify the normally rightward vena cava and leftward abdominal aorta anterior to the spine. Generally, the aorta is typically circular in shape, and the inferior vena cava is triangular. By tracking the course of the inferior vena cava to its junction with the right atrium, visualization of the entire right atrium can be accomplished. Once the right atrium has been identified, the transducer is rotated clockwise along its longitudinal axis until both atria, the interatrial septum, right pulmonary vein, mitral valve leaflets and tricuspid valve anulus are identified. Care must be undertaken in differentiating the eustachian valve from the interatrial septum. The eustachian valve appears to partition the right atrial-vena caval junction into an anterior and posterior compartment.

Echocardiographic Approach to Congenital Heart Disease

The two dimensional echocardiographic approach in patients with complex congenital heart disorders depends on three basic steps.

Great arterial relations: The anatomic relation of the great arteries is best assessed in the parasternal short axis view. The right ventricular outflow tract crosses anterior to the aorta and has a sausage-like appearance (Fig. 2). The pulmonary artery is therefore visualized anterior and to the right of the aorta. By rotating and angulating the transducer in a clockwise manner, the bifurcation of the pulmonary artery can be normally visualized.

In d-transposition of the great arteries, two great arteries are visualized in an anterior-posterior position with the aorta anterior and the pulmonary arterial trunk posterior[9] (Fig. 2). By following each respective vessel, the aorta and pulmonary artery can be differentiated. The pulmonary artery is recognized by its bifurcation into left and right main pulmonary arteries. The aorta is identified as an anterior-situated vessel with a long ascending course, with its three main branches exiting from the aortic arch. In truncus arteriosus, one single great artery is identified and only one circle will be imaged on the cross section.

Ventricular situs: Assessing ventricular situs can usually be accomplished by imaging the ventricles in the short axis views. Anatomically, the mitral valve is found in the morphologic left ventricle and the tricuspid valve in the morphologic right ventricle. The mitral valve can be identified as two leaflets that resemble an ellipse in diastole to the left of the septum. The tricuspid valve has a more anterior attachment than the mitral valve on cross section and may appear triangular in shape during diastole, and never has the appearance of an elliptically shaped structure.

Relation of the great arteries to ventricles, A-V valves and septum: Initially, Henry et al.[9,10] employed a novel technique to determine the connections between the great arteries and the ventricles. The first step consisted of cross-sectioning of the heart at the base of the left-sided ventricle, that is, at the tip of the leaflets of the left-sided A-V valve. The ventricular septum is then identified. The transducer is then angled in a cephalad direction until the origins of the great arteries are identified. These images are recorded on videotape and replayed for analysis. With the image of the ven-

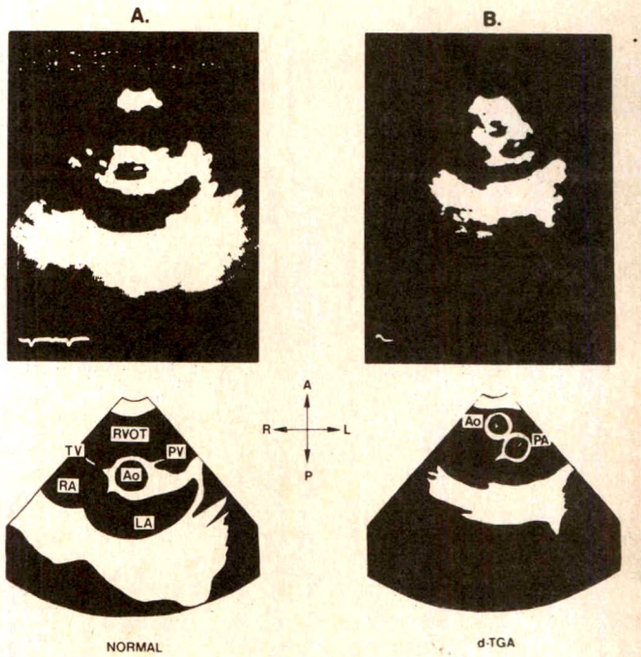


FIGURE 2. A, parasternal cross-sectional view in a normal patient showing the aorta (Ao) and the relation of the right ventricular outflow tract (RVOT) and pulmonary valve (PV) anterior to it. The classic circle and sausage-shaped structures are evident. **B,** parasternal cross-sectional view in a patient with d-transposition of the great arteries (d-TGA). The aorta is anterior and to the right of the circular pulmonary artery. A = anterior; P = posterior; other abbreviations as in Figure 1.

tricular septum on the video screen, the tape recorder is moved frame by frame until a late diastolic frame is obtained. A transparent plastic sheet is taped over the video screen and the right and left surfaces of the ventricular septum are traced. The tape recorder is then advanced until a late diastolic image of the origins of the great arteries is seen. The outline of the ventricular septum on the plastic sheet is then compared with the image of the great arteries, thus allowing the spatial relations between the great arteries and ventricles to be determined. In normal subjects, the aorta originates posterior and to the left of the ventricular septum. In tetralogy of Fallot, the aorta is displaced anteriorly and to the right so that it overrides the ventricular septum. Similarly, in double outlet right ventricle, both great arteries originate anterior and to the right of the ventricular septum. Technique is most important in comparing the position of the great arteries and the ventricular septum during late diastole. Malplacement of the transducer may produce inaccurate information about the degree of overriding.

Although the approach of Henry et al. is a useful one, it is not always practical. Overriding of the aorta can be readily detected in the parasternal and apical long axis views. In addition, precise relations of the great artery in relation to the ventricular chambers can be readily assessed with the apical four chambered view.

Clinical Application

Utilizing the three basic echocardiographic approaches—namely, great arterial relations, ventricular situs and the relation of the great arteries to the ventricles, A-V valves and ventricular septum—complex cyanotic congenital disorders can be readily evaluated.

Tetralogy of Fallot: The anatomic abnormalities in tetralogy of Fallot consist of right ventricular hypertrophy, overriding aorta, ventricular septal defect, and various degrees of pulmonary stenosis. Two-dimensional echocardiography has been found to be more reliable than M mode echocardiography in the evaluation of patients with tetralogy of Fallot.[11] The pulmonary valve was recorded in 90 percent of patients with two dimensional echocardiography but in only 26 percent of patients with M mode echocardiography. Two dimensional echocardiography detected the ventricular septal defect in 95 percent of patients, whereas the defect was detected in only 76 percent with the M mode technique. The interventricular septal defect is characterized as an abrupt dropout of septal echoes rather than the normal blending of septal echoes with anterior aortic wall echoes. Aortic overriding was demonstrated in all patients with tetralogy of Fallot on both two dimensional and M mode echocardiography. In the long axis view, normal fibrous continuity is present between the hinge point of the anterior mitral leaflet and the posterior aortic root.

Aortic overriding and a large ventricular septal defect are not specific for tetralogy of Fallot and can occur in truncus arteriosus (Fig. 3A) and in ventricular septal defect with pulmonary atresia. In the short axis view, the narrowed right ventricular outflow tract in tetralogy is anterior to the aorta whereas in pulmonary atresia or truncus arteriosus neither the pulmonary valve nor the right ventricular outflow tract is imaged.[12] In addition, the results of surgery can be reliably evaluated with use of two dimensional echocardiography.[11] In all patients operated on, aortic septal continuity and an increase in the right ventricular outflow tract were demonstrated postoperatively.

Truncus arteriosus: Generally, truncus arteriosus is associated with aortic overriding and normal mitral-aortic valve continuity. On rare occasions, aortic overriding may not always be demonstrated on two dimen-

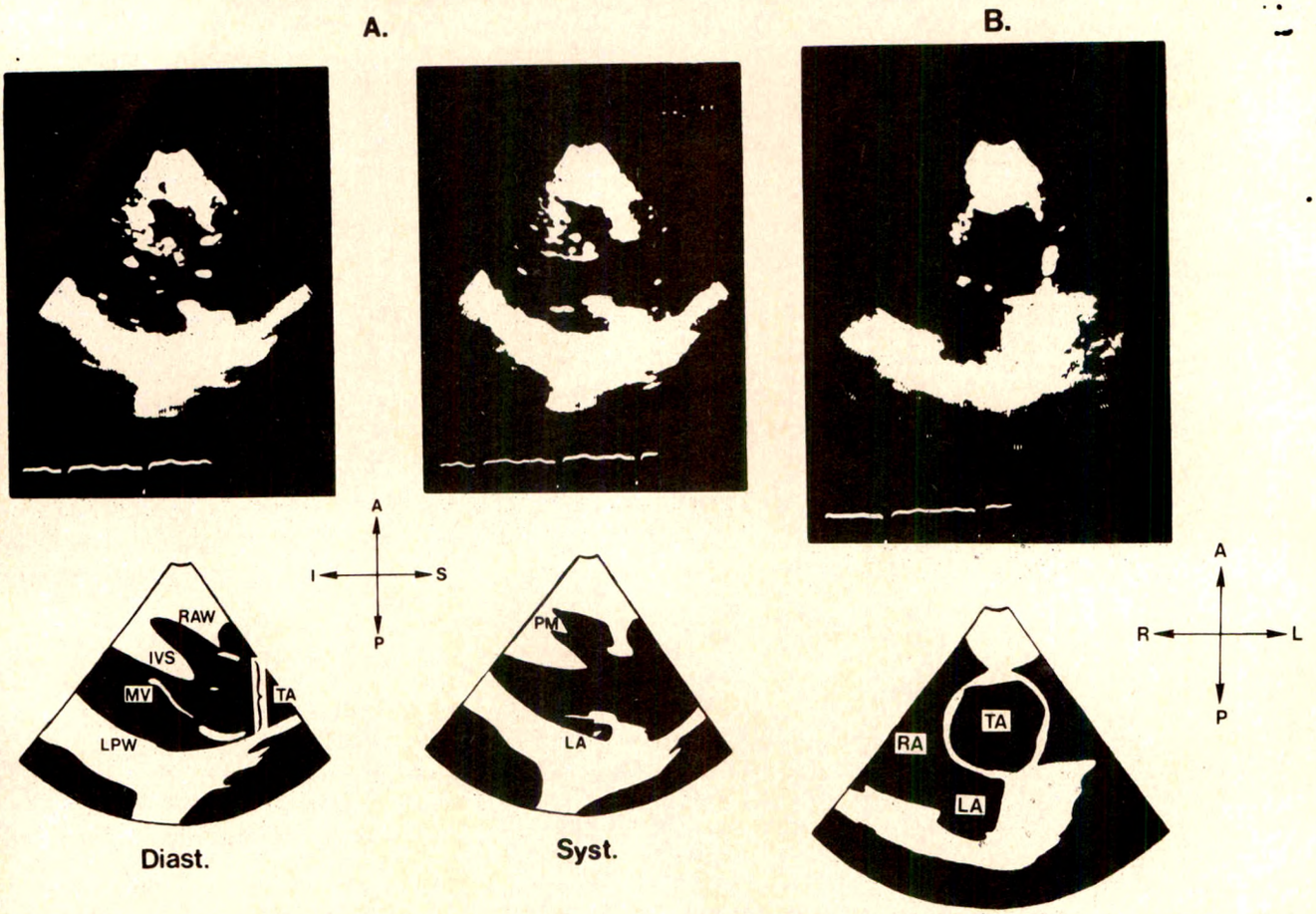


FIGURE 3. A, diastolic (Diast.) and systolic (Syst.) frames obtained in the parasternal longitudinal axis view in a patient with truncus arteriosus showing aortic overriding and a large ventricular septal defect. A large anteriorly situated aorta is apparent with the aortic valve leaflets in the plane of the septum. There is normal mitral (MV) and aortic valve continuity. **B,** same patient. Parasternal cross-sectional view demonstrating single truncus (TA) with absent right ventricular outflow tract and pulmonary valve. LPW = left ventricular posterior wall; PM = papillary muscle; RAW = right anterior wall; other abbreviations as before.

sional echocardiography.[12] A single great artery arises from the left ventricle. In addition, there is an absent right ventricular outflow tract (Fig. 3B). After repair of a truncus arteriosus with a Rastelli operation, thick dense echoes are recorded.[12] These dense echoes represent the ventricular septal patch and are indicative of established continuity of the aorta and the ventricular septum. In addition, the right ventricular outflow tract created by a porcine valve containing conduit is demonstrated around the aorta in a clockwise direction.[12]

Double outlet right ventricle: This is a rare congenital malformation. The pulmonary artery arises in its normal position and the aorta arises from the right ventricle. The great arteries may either be side by side, d-malposed, l-malposed or normally related. A large ventricular septal defect is present but may be above or below the crista supraventricularis. Pulmonary stenosis may or may not be present. The Taussig-Bing anomaly has been used to describe two variations: (1) exclusive right ventricular origin of both great arteries, or (2) right ventricular aorta with biventricular pulmonary trunk, a large ventricular septal defect and absent pulmonary stenosis.[13]

The angiographic and M mode echocardiographic findings rely principally on the demonstration of mitral-semilunar valve discontinuity. However, it is not always possible to recognize discontinuity with M mode techniques. The two dimensional echocardiographic features of double outlet right ventricle have recently been described.[12] In nine patients with double outlet right ventricle who had not been operated on, the characteristic two dimensional echocardiographic finding was the inability to identify any great artery emerging from the left ventricle. In the longitudinal axis view, no continuity existed between the anterior leaflet of the mitral valve and the imaged semilunar valve. This lack of continuity can be identified as an echo-dense area representing left-sided conal tissue between the hinge point of the anterior leaflet of the mitral valve and the posterior margin of the great artery.

In the short axis view, the major observation in seven of nine patients was the ability to visualize both great arteries anteriorly and the ventricular septum posteriorly when sweeping from the left ventricle to the base of the heart. The two dimensional echocardiographic features in patients who have undergone surgery for

double outlet right ventricle consist of a left ventricular outflow tunnel created by the ventricular septal patch and the subaortic conus.

d-Transposition of great arteries: The ventricular situs is normal in this condition and two great arteries leave the heart. The outflow tracts do not cross and the great arteries are parallel. Both mitral-semilunar valve and septal-great artery continuity are present. In the short axis view of the base of the heart, the aorta is directly anterior or anterior and rightward to the pulmonary artery (Fig. 2). No clockwise rotation of the right ventricular outflow tract is observed around the aorta. The medial vessel or pulmonary artery can be identified by scanning in a cephalad and clockwise direction and visualizing its bifurcation into right and left pulmonary arteries.

Frequently, other congenital abnormalities are present in d-transposition of the great arteries; these include tricuspid atresia, single ventricle, endocardial cushion defect and straddling tricuspid valve and should be looked for carefully. The two dimensional echocardiographic feature after repair with the Mustard operation have not been described completely.

Congenitally corrected l-transposition of the great arteries: In this condition, the ventricles are inverted so that the tricuspid valve is to the left of the septum. In the long axis view in patients with congenitally corrected l-transposition, continuity cannot be established between the left-sided systemic A-V valve (the tricuspid valve) and the left-sided (systemic) semilunar valve (aortic valve). When the heart is viewed in cross section, the A-V valve to the left of the septum does not appear to be elliptically shaped in mid diastole but is seen to consist of three leaflets. The elliptically shaped valve in mid diastole is seen to the right of the septum. An increased echo density representing the infundibulum of the right ventricle is observed between the hinge point of the tricuspid valve and the posterior aortic root.[12] In the parasternal short axis or apical view, the great arteries are seen clearly to arise from separate ventricles. In the parasternal short axis view, either the great arteries are visualized in a side by side position or the aorta is anterior and to the left of the pulmonary artery.[12]

Straddling tricuspid valve: Confusion has arisen between the terms straddling and overriding. In one study,[14] overriding describes the relation of the valve anulus to a septum, whereas straddling describes the situation wherein the valve or chordal apparatus is attached to both sides of a septum. In another study,[15] the term malposition of the A-V valves has been used to include all forms of positional abnormalities of the various components of the valve apparatus in relation to its corresponding ventricle. In that study straddling is defined when the valve anulus is displaced in relation to the ventricular septum to lie across the ventricular septal defect with abnormal attachments of portions of the leaflet apparatus to the papillary muscle or to the contralateral ventricular septal surface or to both.[15] The term malattachment is defined as the situation in which no significant anular straddling is present and portions of the leaflet apparatus are attached to the crest of the left ventricular surface of the ventricular septum (septal malattachment) or to the contralateral ventricle (ventricular malattachments). For the purposes of this review, the latter definitions have been adopted.

Two main types of positional abnormalities of the A-V valves were recognized by Aziz et al.,[10] *who used two-dimensional echocardiography and compared the findings with those of angiographic and postmortem studies.* In one group of patients, the A-V anulus straddles the ventricular septum above the contralateral ventricle. In the parasternal long axis view, the tricuspid valve is seen to course from the anterior aspect of the pulmonary artery across the ventricular septal defect into the left ventricle where it is confluent with the mitral valve. In the apical view, the central fibrous body (junction of the A-V anuli) is displaced above the left ventricle. The tricuspid valve opens partly into the left ventricle and partly into the right ventricle. Additional findings include a diminutive right ventricle, a large ventricular septal defect and, on occasion, left ventricular outflow stenosis.

In the other group of patients, the tricuspid valve anulus is normally positioned but septal malattachment of portions of the tricuspid valve to the rim of the ventricular septal defect is present. A ventricular septal defect is present but there is no displacement of the central fibrous body. Similarly, mitral valve malattachment is observed in patients with double outlet right ventricle. The mitral valve leaflet apparatus is abnormally attached to the crest of the ventricular septum as well as to the subpulmonary area.

Atrial septal defect: Because of the great variability in echo dropout of the interatrial septum, in cross-sectional views it may be virtually impossible to distinguish normal subjects from patients with atrial septal defect with two dimensional echocardiography. Use of the precordial and apical positions may compromise visualization of the septum because the ultrasonic beam is not perpendicular to the posterior portion of the interatrial septum. Therefore, artifactual dropout of the echoes from this portion of the septum may occur.[16] Similarly, when the parasternal or apical approach is used, the proximity of the heart and the small size of the cardiac structures make tissue identification difficult in infants.

By employing the subcostal approach, Bierman and Williams[8] were able to evaluate the normal interatrial septum as well as describe various abnormalities in patients with atrial septal defect. Interposition of the liver between the heart and the transducer eliminates the problem of near field imaging due to beam convergence in a sector format. In normal infants with no interatrial communication, the interatrial septum was observed as a straight, linear echo with some central thinning at the level of the foramen ovale. With this approach secundum atrial defects could be differentiated from primum defects. A secundum defect visualized as centrally located, whereas a primum defect is visualized in the lower portion of the interatrial septum. After balloon atrial septostomy, a secundum type defect is created with visualization of flail remnants of the torn septum primum. These investigators can reliably pre-

dict the anatomic defects in the interatrial septum. Utilizing the apical four chambered view, one group of investigators[17] was able to differentiate patients with atrial septal defect from those with mitral stenosis. In patients with atrial septal defect the left atrium was normal in size compared with the observed enlarged left atrium in patients with mitral stenosis.

Ventricular septal defect: Visualization of the usual isolated ventricular septal defect with M mode echocardiography is generally unreliable. Two dimensional echocardiography has been reported[18] to be useful in visualizing the size and location of an isolated ventricular septal defect. Ventricular septal defects appeared as abrupt dropout of septal echoes with broadening of septal edges ("T" artifact) around the defect. The majority of isolated anterior ventricular septal defects could be visualized in the long axis view or intermediate views between the long axis view of the left ventricle and the long axis view of the right ventricle. In the apical four-chambered view, a posterior ventricular septal defect could be best imaged. In parasternal short axis views, which include visualization of the pulmonary valve and mitral valve simultaneously, the detection of a subpulmonary ventricular septal defect could be accomplished. In only 3 of 25 patients was the ventricular septal defect not visualized. Generally, when the ventricular septal defect is less than 5 mm or when the left to right shunt is less than 20 percent, visualization is unlikely.

Septal aneurysm is frequently present in patients who are undergoing spontaneous closure of a ventricular septal defect. Ventricular septal aneurysms have been studied with two dimensional echocardiography.[19] In the long axis and apical views, bulging of the aneurysm and recognition of its origin from the membranous interventricular septum is possible. At times, a tricuspid pouch may have similar two dimensional echocardiographic features.

Patent ductus arteriosus: Direct visualization of the ductus with cross-sectional imaging has been reported.[20] The distal pulmonary artery and its bifurcation are imaged by scanning along the axis of the right ventricular outflow tract. From the scan plane of the main pulmonary artery and its bifurcation, the plane is rotated slightly superiorly so that the ductus arteriosus is directly visualized. This appears to be a promising technique and may provide accurate information with regard to ductal contour and size. However, before it is adopted as a routine procedure, further confirmation by other laboratories in the ability to directly visualize a ductus is essential.

Endocardial cushion defect: *Complete A-V canal:* Endocardial cushion defects can best be appreciated by utilizing the apical and subcostal four chambered views. The presence of a posterior ventricular septal defect near the confluence of the A-V valves and the dropout of echoes from the atrial septum near the confluence are particularly apparent. The parasternal four chambered apical view also allows differentiation of divided and undivided, attached and free-floating common A-V valves.[21] A common A-V valve is usually seen as a single linear echo that crosses the septum and moves as a single valve (undivided) or as two separate valves (divided) during the cardiac cycle (Fig. 4). In the parasternal longitudinal axis view, this common A-V valve leaflet may be frequently seen crossing the plane of the interventricular septum.

Primum defects of partial endocardial cushion defect: In the parasternal longitudinal axis view, the abnormal displacement of the mitral valve into the left

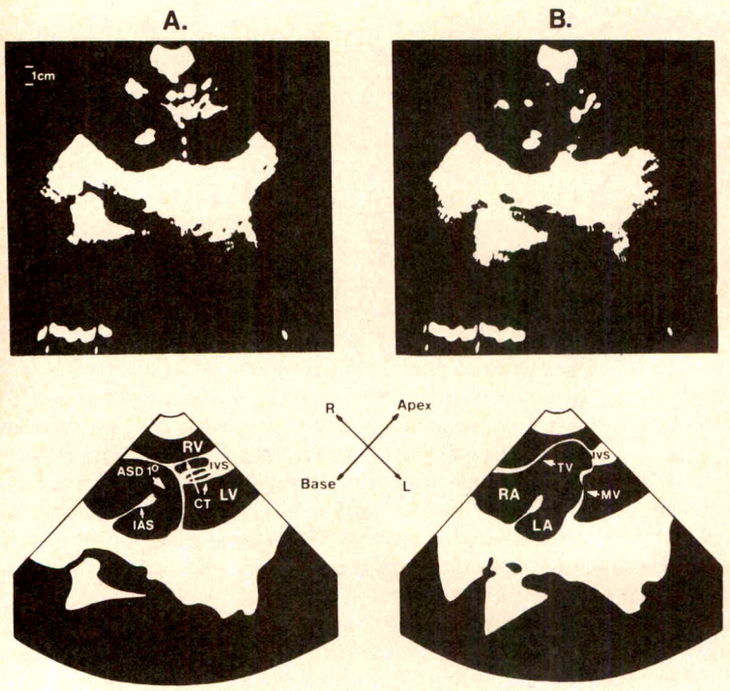


FIGURE 4. Parasternal apical view of a two dimensional echocardiogram in a patient with a complete endocardial cushion defect. A common attached atrioventricular valve that is septally attached (**A**) and appears to be divided during diastole (**B**) is demonstrated. AML = anterior mitral leaflet; ASD 1° = primum atrial septal defect; CT = chordal structures; PML = posterior mitral leaflet; other abbreviations as before.

ventricular outflow tract can be visualized. This is consistent with the so-called gooseneck deformity seen on angiography. In the subcostal view, a defect localized in the lower portion of the interatrial septum is present. Generally, the interventricular septum is intact. In the parasternal cross-sectional view, a cleft in the anterior mitral leaflet can frequently be demonstrated.[22]

Ebstein's anomaly of the tricuspid valve: Two-dimensional echocardiography using the parasternal four chambered apical view allows detection of inferior tricuspid displacement in relation to mitral valve insertion[23] (Fig. 5). The marked inferior displacement of the tricuspid valve with a small right ventricular cavity and a huge atrialized right ventricle is characteristic of Ebstein's anomaly of the tricuspid valve. In addition, associated tricuspid regurgitation and a right to left shunt can be detected with the use of contrast echocardiography. Measurements have been derived to calculate the length of the atrialized right ventricle. By employing the ratio of the mitral valve to apex and the tricuspid valve to apex distances, a value of 1.8 to 3.2 in patients with Ebstein's anomaly was encountered compared with a mean of 1.029 in normal subjects.[23]

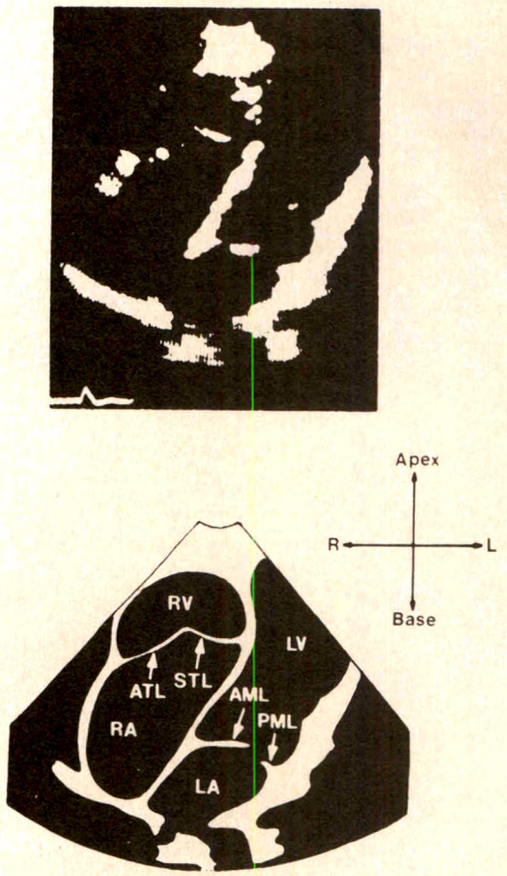


FIGURE 5. Two dimensional echocardiogram obtained in the apical parasternal four chambered view in a patient with proved Ebstein's anomaly of the tricuspid valve. The inferior displacement toward the apex of the tricuspid valve in relation to the mitral valve is visualized. The right ventricle is reduced in size and a large right atrium (RA) or atrialized right ventricle (RV) is also demonstrated. ATL = anterior tricuspid leaflet; STL = septal tricuspid leaflet; other abbreviations as before. (Reprinted from Kotler MN, Mintz GS, Segal BL, Parry WR. Clinical uses of two dimensional echocardiography. Am J Cardiol 1980;45:1061–82.)

Aortic Stenosis

Left ventricular outflow obstruction can be caused by either valvular, subvalvular or supravalvular aortic stenosis. In turn, each of these types can be further subdivided according to etiologic, morphologic or clinical characteristics. The parasternal long axis view of the ascending aorta and left ventricular outflow tract has provided an accurate means of identifying and localizing the level of obstruction. Therefore, differentiation between subvalvular, valvular or supravalvular obstruction is possible.

Aortic valve stenosis: Congenital aortic stenosis may be due to a unicuspid or bicuspid aortic valve. When the valve is unicuspid, obstruction may be present at an early age and survival to adulthood is unusual. Bicuspid aortic valve is the most common congenital cardiac anomaly in adults and it can be accurately identified in 95 percent of patients with two dimensional echocardiography compared with approximately 75 percent by M mode.[24] With use of the short axis view, the exact number of cusps can be seen (Fig. 6). In addition, irregularity in folding of cusp margins and abnormal location of commissural insertion are seen.

In patients with a bicuspid aortic valve, two dimensional echocardiography has been helpful in explaining the variability of findings of M mode echocardiography. In the parasternal longitudinal axis view, the valves dome in systole as well as have an unusual appearance in diastole.[25] The normal aortic valve coapts in diastole and appears as a thin line parallel to and midway between the walls of the aorta. In congenital aortic stenosis this parallel line is not seen. A thick line perpendicular to and connecting the two walls of the aorta is demonstrated in diastole. Although some investigators[25] have correlated the degree of separation of the tips of the leaflet in systole with the aortic gradient, this has not been confirmed by other investigators. Concentric hypertrophy may also be visualized with two dimensional echocardiography.

Subvalve aortic stenosis: *Discrete subaortic stenosis:* Subaortic stenosis may be due to a discrete membrane, fibromuscular ridge or collar, and fibromuscular tunnel. The lesions are all localized to the left ventricular outflow tract. Because the transducer is frequently parallel to the subaortic membrane it can be only rarely visualized with M mode echocardiography. With use of two dimensional echocardiography, discrete subvalvular membranes or a fibromuscular type of subaortic stenosis can be evaluated. The membranous type, which is the most common, is recognized as a distinct linear echo or mass of echoes within the outflow tract. In addition, the membrane may exhibit dynamic motion which can readily be appreciated with two dimensional echocardiography. Patients with a fibromuscular lesion demonstrate a diffuse or shelf-like narrowing of the outflow tract. Postoperatively, these lesions may disappear completely.

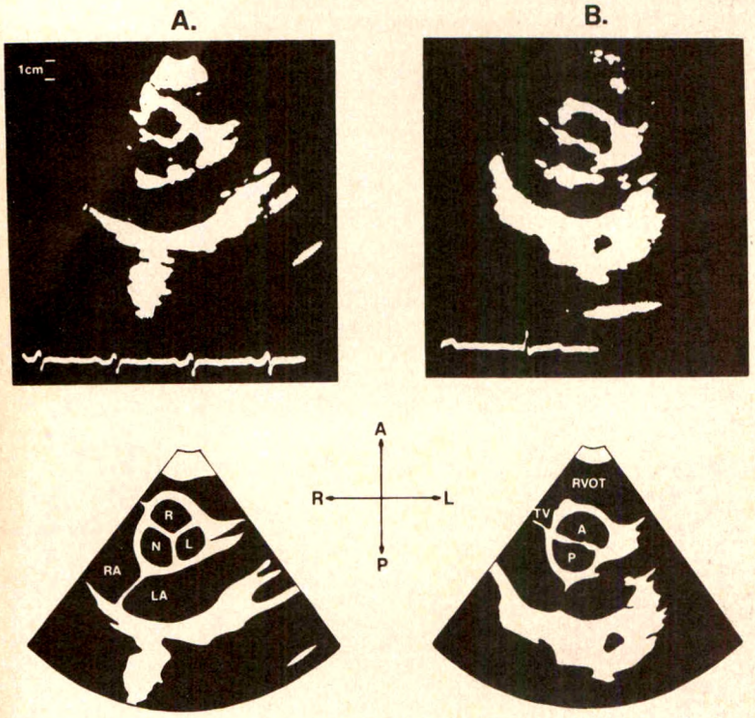


FIGURE 6. A, parasternal cross-sectional view in a patient showing the normal trileaflet aortic valve. **B,** parasternal cross-sectional view in a patient with a bicuspid aortic valve. An anterior (A) and posterior (P) leaflet are separated by a single commissure. L = left coronary cusp; N = noncoronary cusp; R = right coronary cusp; other abbreviations as before.

Idiopathic subaortic stenosis or hypertrophic obstructive cardiomyopathy: The thickened septum as well as systolic anterior motion of the mitral valve can readily be visualized in patients with idiopathic hypertrophic subaortic stenosis. This entity will be discussed elsewhere in the Symposium.

Supravalve aortic stenosis: Supravalve aortic stenosis is an uncommon malformation with heterogenous anatomic features and a large incidence of associated congenital heart defects. Cross-sectional echocardiography was shown to be useful in visualizing the area of obstruction in patients with supravalve aortic stenosis.[27] The echocardiographic localization of site of obstruction correlated well with the angiographic findings. The hourglass, hypoplastic and membranous types can be differentiated with two dimensional echocardiography.

Coarctation of the aorta: With the suprasternal approach, visualization of the coarcted segment of the aorta was reported in 16 of 18 patients studied with two dimensional echocardiography.[28] The coarcted segment is generally recognized as a localized area of narrowing, usually distal to the left subclavian artery (Fig. 7). In addition, prominent systolic pulsation and expansion of the aortic arch and left subclavian vessel proximal to the coarctation are seen.

Pulmonary stenosis: The pulmonary valve can be visualized in the parasternal short axis view. Normally, the pulmonary leaflet echoes move rapidly apart during systole and, when fully opened, lie parallel and in close apposition to the margins of the pulmonary artery. Complete recording of the pulmonary valve leaflets may not always be possible. In pulmonary valve stenosis, doming and restriction of motion are present.[29] In addition, infundibular stenosis of the right ventricular outflow tract may be visualized from a subcostal approach.[30]

Tricuspid atresia: Tricuspid atresia is suggested in the short axis view by recording a single A-V valve. In the long axis view, the valve is in fibrous continuity with the posterior margin of the great vessel, thus identifying it as a mitral valve. Generally, dense echoes are recorded in the vicinity of the tricuspid valve but no discrete tricuspid valve echo motion may be identifiable.[31] In patients with tricuspid atresia, the left ventricle is large and the right ventricle is diminutive or small and may even be absent. A large ventricular septal defect is generally present.

Pulmonary atresia with intact septum: The right ventricle may be large and the tricuspid valve waveform is distorted and of low amplitude.[32] In the short axis view, a pulmonary valve cannot be identified.

Hypoplastic left heart syndrome: This syndrome includes aortic atresia, mitral atresia with or without a ventricular septal defect, and aortic stenosis. In the long axis view, the aortic root is diminutive or absent, the mitral valve echo is distorted or immobile and the posterior ventricle is small whereas the anterior ventricle is large.[32] A large tricuspid valve is identified. In variations of this syndrome, such as mitral atresia with a ventricular septal defect or critical aortic stenosis, modification of the two dimensional echocardiographic features is present.[32]

Cor triatriatum: The membrane can be demonstrated in the parasternal apical view since it lies within the left atrium just superior to the mitral valve.[32] In addition, a supravalve mitral stenosing ring may also be detected.

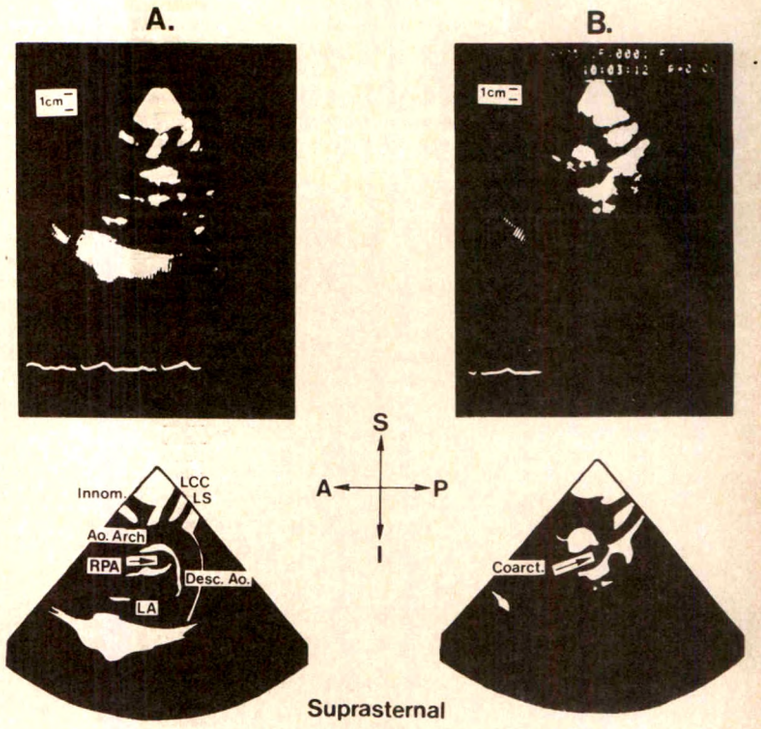


FIGURE 7. Suprasternal views of a two dimensional echocardiogram of the aortic arch in a normal subject (**A**) and in a patient with coarctation (**B**). In the normal subject (**A**), the aortic (Ao) arch and its branches are visualized. The narrowed segment in coarctation (Coarct.) of the aorta is clearly visualized in **B**. Innom = right innominate artery; Desc. Ao. = descending aorta; LCC = left common carotid artery; LS = left subclavian artery; other abbreviations as before. (Reprinted from Kotler MN, Mintz GS, Segal BL, Parry WR. Clinical uses of two dimensional echocardiography. Am J Cardiol 1980;45:1061–82.)

Localization of the coronary sinus and descending aorta in congenital heart disorders: Conditions resulting in an increased coronary sinus blood flow will produce an enlarged coronary sinus.[33] The most common congenital anomalies of the coronary sinus include a persistent left superior vena cava draining into the coronary sinus and total anomalous pulmonary venous connection to the coronary sinus. The M mode features of an enlarged coronary sinus include a dense echo posterior to the mitral valve at the level of the A-V junction with a clear space behind this dense echo.

The two dimensional echocardiographic features of an enlarged coronary sinus include a distinct circular structure lying posteriorly in the A-V junction, best visualized in the parasternal long axis view.[33] In two patients with total anomalous pulmonary venous connection, the confluence of the pulmonary veins and their connection to the coronary sinus were imaged in the long axis plane. Great care should be undertaken in differentiating an enlarged coronary sinus from the descending aorta[34,35] and the parasternal short axis views may prove helpful in this differentiation. In the short axis views, the course of the descending thoracic aorta can be followed.[34] At the level of the tips of the mitral leaflets or of the papillary muscles, the descending aorta first appears as a posterior circular or oval echo-free space. At the level of the mitral leaflets, it is located directly behind the left ventricle. At the level of the left atrium, it is seen lateral to and behind the left atrium, and at the level of the pulmonary arterial bifurcation, it appears directly posterior to the bifurcation. In normal infants, the descending thoracic aorta is not visualized in close proximity to the left atrial and left ventricular posterior walls.[35] However, in infants with significant arteriovenous malformations, enlargement of the heart and descending aorta occur resulting in the left atrial and left ventricular posterior walls approximating the descending aorta.[35]

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Radionuclide Angiography in Congenital Heart Disease

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Cardiac nuclear imaging (radionuclide angiography, electrocardiographic gated ventriculography and myocardial scintigraphy) provides structural and functional information simultaneously. This method extracts accurate quantitation of cardiovascular hemodynamics and unique information regarding myocardial perfusion. It is a reliable and relatively simple and atraumatic technique because the only discomfort to the patient is a simple intravenous injection. These studies are carried out rapidly in out- or inpatients. Radionuclide angiography is ideal also to assess the effect of exercise, oxygen or drugs on cardiac function. The radiation exposure associated with current nuclear imaging is within the range of common radiographic procedures and many times lower than that of cardiac catheterization. The use of newer radionuclides such as iridium-191m with a physical half-life of 4.96 seconds will result in a dramatic decrease in the radiation exposure to patients undergoing radionuclide angiography. Also, newer and smaller computerized gamma cameras will provide studies of improved spatial resolution and accuracy. The future of pediatric applications of cardiac nuclear imaging is bright.

Cardiac nuclear imaging and cross-sectional echocardiography help evaluate the structure and function of the cardiovascular system. Their combined use permits the cardiologist to acquire information about the heart that previously could be obtained only by cardiac catheterization. Significant progress in the technology and clinical applications of these noninvasive methods is occurring at an impressive rate. Close collaboration of cardiologists and specialists in nuclear medicine is essential for cardiac nuclear imaging to reach its potential.

Radionuclide angiocardiography and echocardiography can provide equivalent or complementary data. Echocardiography can image an atrial septal defect whereas radionuclide angiography can measure the actual shunt flow. Echocardiography can determine myocardial wall thickness whereas thallium-201 scintigraphy defines the distribution of myocardial blood flow.

Cardiac Nuclear Imaging

Cardiac nuclear imaging is performed with use of radiopharmaceuticals and computerized gamma cameras. There are three main techniques of cardiac nuclear imaging: first pass radionuclide angiography, electrocardiogram-gated angiography and thallium-201 myocardial scintigraphy.

First Pass Radionuclide Angiography

A single small bolus dose of a radiopharmaceutical is given intravenously in first pass radionuclide angiography. Imaging is carried out at rates of 1 to 100 frames/s for 20 to 40 seconds. The series of images depict the bolus injection of radioindicator as it circulates within the heart, lungs and great vessels.[1–10] The study is examined visually for anatomy. A numerical analysis of dilution curves can be obtained from almost any place in the cardiovascular system (Fig. 1). The radionuclide used most commonly for angiography is technetium-99m (physical half-life, 6 hours; photon energy, 140 keV) as sodium pertechnetate. The radiation absorbed with this procedure is relatively low[11] (Table I). To date there

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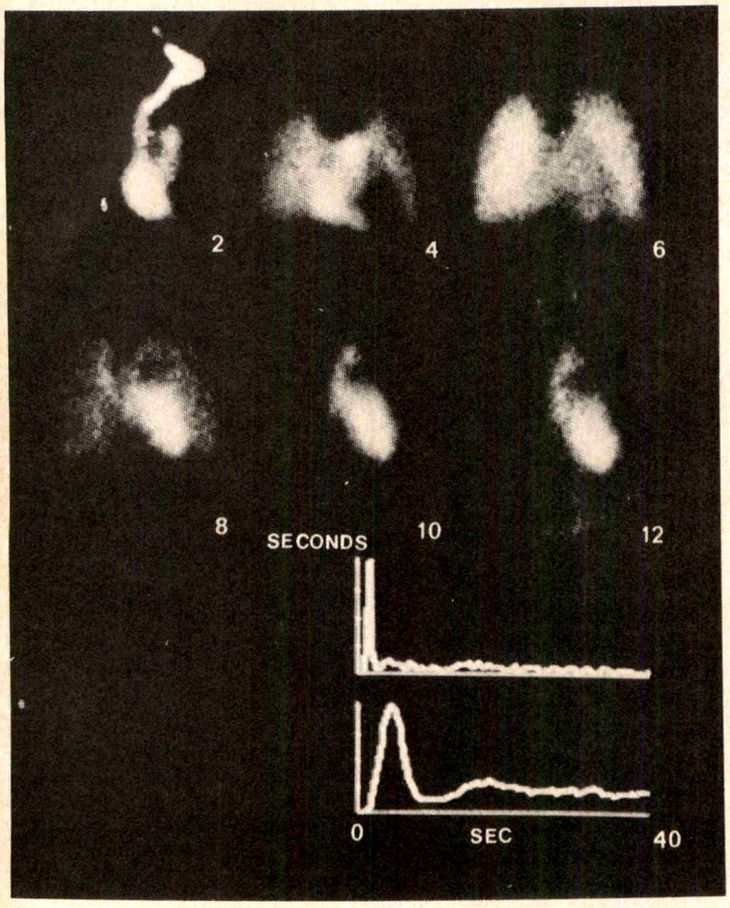


FIGURE 1. Normal radionuclide angiogram, anterior view. Series of frames reveal radionuclide circulation in the superior vena cava, right side of the heart, pulmonary artery, lungs, left side of the heart and aorta. Time-activity curves of the superior vena cava and the right lung are shown **below.**

has been no evidence of any early or late effects secondary to the administration of diagnostic doses of technetium-99m radiopharmaceuticals in human beings or animals.

Left to right intracardiac shunts: Technetium-99m pertechnetate is used in the detection and quantitation of shunts.[12–22] To detect left to right shunts a series of images in the anterior or left anterior oblique projection is obtained at 2 or 4 frames/s for 25 seconds. The patient can be studied supine or upright. A visual analysis of the angiogram is carried out to assess the flow of the radioindicator through the cardiopulmonary system and to define regions of interest for the calculation of time-activity curves. These regions are marked on the computer display over the superior vena cava and each lung. The curve from the region of interest over the superior vena cava serves to assess the input bolus curve.[2] The curve should have a single peak that should last less than 3 seconds (Fig. 1). A normal radionuclide angiogram shows the radioindicator as it circulates within the superior vena cava, right atrium, right ventricle, pulmonary artery, lungs, left atrium, left ventricle

TABLE I

Radiopharmaceuticals for Cardiac Imaging

Radiopharmaceutical	Administered Dose (mCi) mCi/kg	Minimal Total Dose	Radiation Absorbed Dose (rad)* Whole Body	Critical Organ	
Tc-99m sodium pertechnetate	0.200	2.0	0.110–0.182	Intestine	1.3–2.8
Tc-99m human serum albumin	0.200	2.0	0.124–0.210	Blood	0.48–0.70
Tc-99m red blood cells	0.200	2.0	0.124–0.210	Blood	0.48–0.70
Tc-99m macroaggregated human serum albumin	0.030	0.2	0.013–0.030	Lung	0.20–0.40
Tc-99m pyrophosphate	0.050	0.2			
Tl-201 thallous chloride	0.300	0.25	0.25–0.36	Kidney	1.1–2.4

* Absorbed doses given to a 1 year old and an adult patient. Tc-99m = technetium-99m (physical half-life 6 hours; principal gamma ray 140 keV); Tl-201 = thallium-201 (physical half-life 73.3 hours; principal photon energies 60–80, 135 and 168 keV).

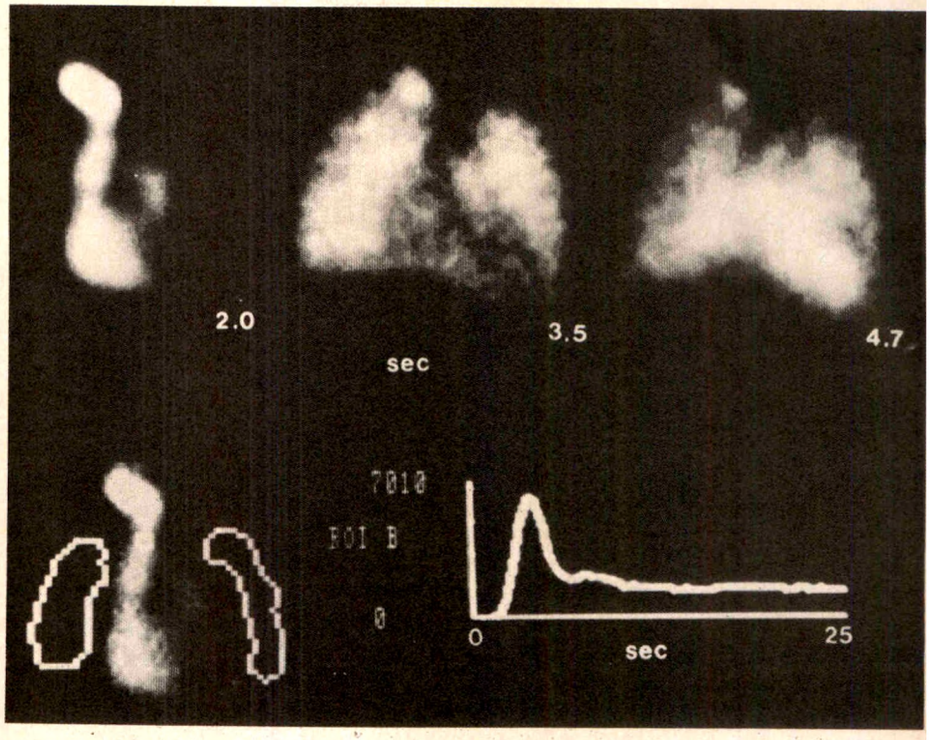


FIGURE 2. Left to right shunt. Selected frames from an anterior radionuclide angiogram demonstrate persistent activity in the lung fields and poor visualization of the left side of the heart (4.7 sec). Regions of interest are marked over the lung fields (**lower left panel**) and the pulmonary time-activity curve reflects early pulmonary recirculation due to the left to right shunt (**lower right panel**).

and aorta. The normal pulmonary curve has a characteristic appearance (Fig. 1). In a left to right shunt there is an early pulmonary recirculation peak on the curve (Fig. 2). In a large shunt there often is reduction of the activity in the right side of the heart as the radioindicator is diluted with unlabeled blood passing through the defect. Later frames show persistence of activity within the lung fields. There might be poor visualization of the left ventricle and the aorta, and the right side of the heart is often enlarged. In addition, in left to right shunting, the transpulmonary transit time is more rapid than normal.

With careful selection of small regions of interest it is possible to determine the level of the shunt. In situations in which there are multiple levels of left to right shunting, only the most proximal level can be detected with this approach.[23] In surgically produced palliative shunts (Potts, Blalock-Taussig, Waterston), the recirculation seen in the lung receiving the shunt is greater than that in the other lung.[24] In patent ductus arteriosus, the left pulmonary curve often reveals greater recirculation than the right.

Quantitative analysis of the pulmonary curve can determine the pulmonary to systemic flow ratio (Qp: Qs). One method developed in our laboratory[20] uses a mathematic model to separate the activity due to the first pulmonary transit of the radioindicator from that caused by the shunt (Fig. 3). The gamma variate function is used to "dissect" the pulmonary curve into two components representing single passes of the radioindicator. A gamma variate fit of the initial segment of a pulmonary curve in left to right shunting represents the first circulation of the radioindicator through the pulmonary vasculature (Qp = pulmonary flow). The area defined by the gamma variate (A_1) is subtracted from the rest of the pulmonary curve and another gamma variate is fitted to the initial portion of this new curve, defining a second area (A_2). Area A_2 reflects early recirculating activity in the lungs due to left to right shunting of the labeled blood. If area A_2 is subtracted from area A_1, the area that remains is proportional to the systemic flow ($A_1 - A_2 = Qs$). A ratio of areas $A_1/A_1 - A_2$ represents the pulmonary to systemic flow ratio (Fig. 3 and 4c). This method was found accurate for the calculation of Qp/Qs between 1.2 to 3.0 ($r = 0.94$).[20–22,25] The reduced accuracy between Qp/Qs of 1.0 and 1.2 may reflect the normal chest wall and bronchial arterial circulation that are "seen" by the detector. Shunts of Qp/Qs greater than 3 are detected but cannot be quantified because adequate gamma variate fits to the pulmonary curve are not obtained. Crying and Valsalva

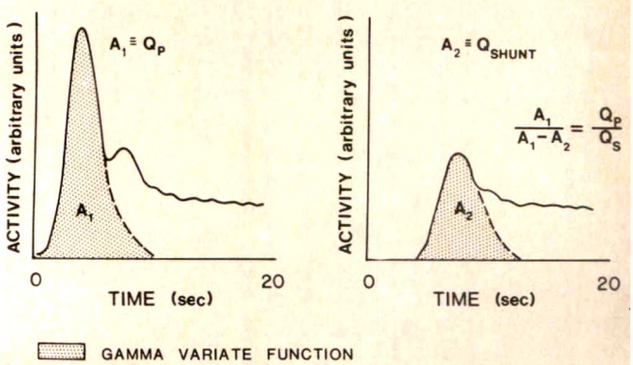


FIGURE 3. Method for quantitation of left to right shunts. A pulmonary curve is analyzed using a gamma variate model. See text.

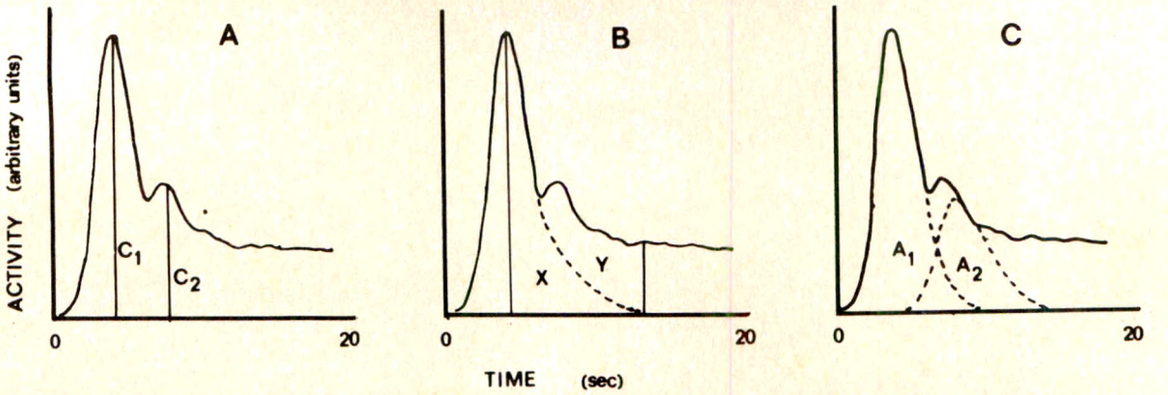


FIGURE 4. Methods for analysis of pulmonary curves in left to right shunting. **A,** the C_2/C_1 method of Folse and Braunwald.[14] A ratio of the amplitudes at the peak and at another point at twice the distance between the appearance of the activity in the lungs and the peak is used. **B,** area ratio x/y method of Anderson et al.[13] **C,** the Qp:Qs ratio method of Maltz and Treves.[20]

maneuvers, pulmonary regurgitation and the presence of significant bronchial or intercostal collateral vessels and right to left shunting may preclude accurate quantitation of shunts.

Another method developed by Anderson et al.[13] *also analyzes the pulmonary curve* (*Fig. 4B*). An area, Y, is defined as that resulting from logarithmic extrapolation of the initial portion of the downslope to a point at 1 percent of the peak and a line from the peak to the baseline. Another area, X, is defined as the area between the actual and the extrapolated curves to a vertical line traced at the l percent point. The percent of left to right shunting is calculated using a ratio X/Y. Using a quadratic regression, Anderson et al. found a good correlation with shunt flow ($r = 0.95$) measured during cardiac catheterization.

Folse and Braunwald[14] *suggested a method for the detection of left to right shunts using the pulmonary time-activity curve.* The peak of the curve is identified as C_1 (Fig. 4A). To define C_2, the time from the initial appearance of tracer in the lung to the peak of the activity is measured. This time is doubled and C_2 is plotted as the activity appearing at this later time. A high ratio, C_2/C_1, indicates the presence of a left to right shunt. Although this is a simple method, identical values of C_2/C_1 have been found in patients with and without left to right shunts.[20]

Right to left shunts: Right to left shunting can be detected on first pass radionuclide angiography by the premature appearance of the radionuclide in the left side of the heart and the aorta. A time-activity curve from the left ventricle can be analyzed for quantitation of right to left shunting. A first peak of activity due to blood shunted from right to left is followed by a secondary peak due to radioactivity that circulated through the lungs. With use of an exponential extrapolation to the baseline after the first peak and another after the second peak, the pulmonary to systemic flow ratio can be estimated as the ratio of the area under the first peak to the area under both peaks.[15]

An alternative method for detecting and measuring right to left shunting is intravenous technetium-macroaggregated albumin. In the normal circulation, more than 95 percent of all particles are trapped in the pulmonary capillaries.[5] In right to left shunting (extracardiac or intracardiac) a much greater portion of the particles will reach the systemic capillary bed. The pulmonary to systemic flow ratio is calculated by dividing the pulmonary activity by the activity in the whole body, including the lungs. Although published data suggest a wide margin of safety with this method, concern still exists regarding possible microembolization of systemic end arteries.

Ventricular ejection fraction: Right and left ventricular ejection fraction can be measured by first pass radionuclide angiography using technetium-99m pertechnetate.[25–29] When recording at rapid frame rates (that is, 20 frames/s) it is possible to define end-systole and end-diastole in the angiogram without electrocardiographic gating. The oscillations on the time-activity curve from the ventricle are due to changes in intraventricular volume during the heart cycle. Images for end-diastole and end-systole can be obtained by selecting the appropriate frames. The ejection fraction (EF) can be measured by the following formula:

$$EF\ (\%) = \frac{EDC - ESC}{EDC}$$

where EDC = end-diastolic count and ESC = end-systolic count.

Cardiac output: In another technique of first pass radionuclide angiography technetium-99m human serum albumin is used to determine cardiac output (Fig. 5). Cardiac output can be calculated by analysis of a time-activity curve obtained from a region of interest marked over the heart.[30] A semilogarithmic extrapolation of the downslope of the segment of the curve corresponding to the activity in the left heart is used to determine an area (A). To correct for the cardiac blood volume viewed by the detector, a count rate is recorded at the time of equilibrium (e) of the radioindicator in the blood. The total blood volume (TBV) is determined by an independent method and the cardiac output (CO) is calculated as follows:

$$CO = (ml/min) = (TBV \times e)/A$$

Gated Blood Pool Radionuclide Ventriculography

This technique of nuclear imaging[31–37] requires the use of an intravascular indicator, most commonly technetium-99m human serum albumin or technetium-99m red blood cells. The radiophomaceutical is given intravenously and recording starts 5 minutes later. Each heart cycle is divided into a series of consecutive frames by electrocardiographic gating. Several hundred (100 to 500) heart cycles are added together on the computer's memory, and a series of images representing an average heart cycle is recorded. On playback the study is reconstructed into a series of images in an average heart cycle.

The series of images is analyzed visually to detect abnormalities in cardiac structure and ventricular wall motion or to measure chamber size. Time-activity curves are calculated from selected regions over the ventricles. The changes in the count rate in these curves relate to changes in intracardiac volumes. Analysis of these tracings permits evaluation of ventricular ejection fraction and ejection and filling rates. Ventricular volume and cardiac output also can be calculated with this method. Because the radiopharmaceutical remains in in the blood pool, multiple gated scans are possible over a period of hours. Thus, the short-term effect of exercise or drugs on cardiovascular function can be evaluated.[37,38]

Thallium-201 myocardial perfusion scintigraphy: Thallium-201 is produced in the cyclotron (half-life, 73.3 hours; principal photon energies, 60 to 80, 135 and 168 keV) and is a potassium analog.[39–44] After intravenous injection, thallium-201 concentrates rapidly in many organs including the thyroid, myocardium, liver, kidneys and muscle. Imaging is begun almost immediately after injection. Images are obtained in multiple projections and are analyzed visually using computer processing.

When thallium-201 is injected with the patient at rest, about 3 percent of the injected dose is taken up in the heart. Its myocardial distribution is proportional to the regional coronary blood flow. The right ventricle normally is not visualized. During exercise there is redistribution of thallium-201 corresponding to redistribution of blood flow. If thallium-201 is injected during exercise hepatic uptake is reduced, myocardial uptake increases and the right ventricle is visualized. Areas of myocardial ischemia that might not be detected when the patient is examined at rest could become apparent during exercise.

Echocardiography

M mode and two dimensional echocardiography are studies that complement each other and cardiac nuclear imaging. Subxiphoid two dimensional echocardiography, a noninvasive technique, provides good anatomic resolution down to 1 mm dimensions in infants and small children; thus many atrial septal defects[45] and ventricular septal defects[46] are visible with this technique. Complex malformations such as transposition of the great arteries, total anomalous pulmonary venous return, tetralogy of Fallot, tricuspid atresia, hypoplastic left heart, idiopathic hypertopic subaortic stenosis and

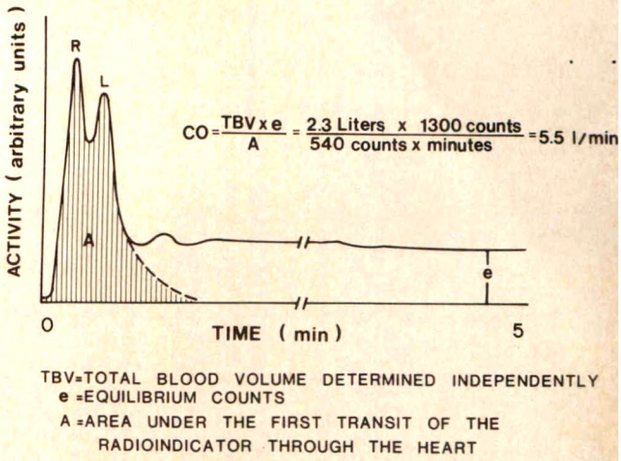


FIGURE 5. Method for determination of cardiac output. Time versus activity curve obtained over the heart as technetium human serum albumin-99m circulates within the right side (R) and then the left side (L) of the heart. Equilibrium (e) in the blood pool is reached a few minutes later. The total blood volume (TBV) has been determined by using iodine-125 human serum albumin.

Ebstein's anomaly also can be detected with this technique. Although valve anomalies sometimes are visualized, quantitation of stenosis and regurgitation is not possible.

Techniques for measuring ejection fraction, cardiac output and other indexes of left ventricular function are well developed using one dimensional (M mode) echocardiography. Echocardiography also can provide indirect evidence of intracardiac shunts.[47] Contrast echocardiography is useful particularly in detection of right to left shunts but quantitation of shunt flow is not yet possible.[48] Patients undergoing echocardiography are exposed to ultrasonic radiation. To date harmful effects have not been reported in human subjects. Echocardiographic studies can be performed serially, the equipment is mobile, and most examiners can complete a study in about 10 minutes.

Cardiac Catheterization and Angiography

All new methods for diagnosis of congenital heart disease are compared with cardiac catheterization for accuracy and completeness. Anatomic resolution is excellent although not infallible. This is the only method other than surgery that permits the direct measurement of intracardiac oxygen saturation and pressures. Good quantitation of left and right ventricular function is possible. The equipment for cardiac catheterization is not mobile, the patients usually are hospitalized and the procedure is invasive. Risks include damage to blood vessels, thrombosis, hemorrhage, arrhythmia, infection and fatal cardiac arrest.[49] The contrast material is injected under high pressure. In small infants with severe congestive heart failure the volume of contrast material required could result in fluid overload. The osmolality of the contrast material can produce transient physiologic alterations or arrhythmias, or both. The procedure takes 1 to 2 hours and radiation exposure can be considerable.

TABLE II

Cardiac Nuclear Imaging in the Evaluation of Patients in the Postoperative Period

1. Detection and quantitation of residual shunts (ASD, VSD, PDA, Mustard, Senning, etc.)
2. Determination of the patency of palliative shunts (Waterston, Potts, Glenn, Blalock)
3. Determination of the patency of vascular grafts (Fontan)
4. Assessment of patency of the superior or inferior vena cava (Mustard, precatheterization)
5. Measurement of cardiac function (ejection fraction, end-diastolic volume, cardiac output)
6. Evaluation of intracardiac blood mixing after balloon atrial septostomy in TGA
7. Detection of myocardial ischemia and infarction

ASD = atrial septal defect; PDA = patent ductus arteriosus; TGA = transposition of the great arteries; VSD = ventricular septal defect.

Clinical Applications

The Premature and Newborn Infant

Patent ductus arteriosus: At least 15 percent of all premature infants with a birth weight less than 1,800 g have a hemodynamically significant patent ductus arteriosus.[50] The diagnosis of patent ductus arteriosus is made by clinical examination (systolic or continuous murmur, wide pulse pressure, tachycardia and often congestive heart failure). It is believed that the left to right shunt through a patent ductus arteriosus even without clinically evident congestive heart failure may prolong and complicate the course of respiratory distress syndrome. Some infants with a patent ductus arteriosus and congestive heart failure can require prolonged artificial ventilation.

It is difficult to identify those patients with the respiratory distress syndrome and a patent ductus arteriosus who will benefit from reduction of flow across the ductus. The intensity of the murmur is an unreliable indicator of the magnitude of left to right shunting. An indirect measurement of shunt flow is the ratio of the left atrial to the aortic root dimensions as determined with M mode echocardiography.[51] Radionuclide angiography is used to measure the left to right shunt directly. This information often aids in determining therapy.

Pulmonary versus cardiac disease: In the newborn, the use of radionuclide angiography need not be limited to quantifying known shunts; the technique may also assist in distinguishing pulmonary from cardiac disease. After ligation of a patent ductus arteriosus the condition of some infants with respiratory distress syndrome continues to deteriorate. This deterioration can be the result of persistent severe lung disease or a complication of the surgical technique. Radionuclide angiography can be invaluable in determining the diagnosis. A normal study with no residual left to right shunt would strongly suggest a pulmonary cause for the persistent problems. The persistence of a left to right shunt with equal perfusion in the left and right lungs would suggest either incomplete ligation of the patent ductus arteriosus or the presence of additional, previously unsuspected cardiac defects (for example, aortic pulmonary window or ventricular septal defect). The persistence of a large left to right shunt without visualization of the left lung suggests inadvertent ligation of the left pulmonary artery at the time of the attempted ductal ligation. (Table II).

Ventricular septal defect: In newborns with ventricular septal defect alone, a radionuclide angiogram may appear normal because of a relatively high pulmonary vascular resistance and the resultant small left to right shunt. As the pulmonary vascular resistance decreases, left to right shunting increases and the radionuclide angiogram reveals the shunt.[2]

Right ventricular hypertrophy: In the newborn, relative right ventricular hypertrophy secondary to the high pulmonary vascular resistance usually will permit thallium-201 visualization of the right ventricle immediately after birth. In normal older children, the right ventricular uptake of thallium-201 is almost imperceptible in studies performed at rest. It is possible with thallium-201 to quantitate right ventricular hypertrophy in patients with pulmonary stenosis, left to right shunts with secondary pulmonary hypertension and chronic lung disease. In exercise studies, the right ventricle is seen and this should not be considered abnormal.

Myocardial ischemia and infarction: Thallium-201 scintigraphy has been used to evaluate regional myocardial perfusion in newborn infants suspected of having an anomalous origin of the left coronary artery from the pulmonary artery.[52] In these instances, the radioactive thallium will have little or no concentration in the area of affected myocardium. Thallium-201 is useful in the noninvasive differentiation of anomalous left coronary arterial from congestive cardiomyopathy. In mucocutaneous lymph node syndrome there can be decreased thallium-201 uptake secondary to ischemia or myocardial infarction. Emission computed tomography using thallium-201 appears to increase the sensitivity of this method of myocardial imaging in small children.[53]

The evaluation of right and left ventricular function using first pass radionuclide angiography[29] and equilibrium gated studies is possible in infants but it has not been used extensively.

Older Infants and Children

Atrial septal defects: Patients with a secundum atrial septal defect have characteristic findings on physical examination, chest X-ray film and electrocardiography. In our institution surgical closure of these defects is undertaken in most cases without cardiac catheterization. If confirmation of the diagnosis becomes necessary, the combined use of subxiphoid two dimensional echocardiography and radionuclide angiography can localize the defect and quantitate the shunt

flow. These two methods may also be helpful in those cases in which it is difficult to differentiate between a small atrial septal defect and mild pulmonary stenosis. One limitation of radionuclide angiography is that it often cannot differentiate between atrial septal defect and partial anomalous pulmonary venous return.

Ventricular septal defect: Most patients with the clinical diagnosis of a small ventricular septal defect need not undergo diagnostic imaging. However, if confirmation is desired, subxiphoid two dimensional echocardiography might visualize the defect in infants and small children and radionuclide angiography can quantify a shunt reliably if Qp/Qs is more than 1.2. Serial quantitation of left to right shunt flow in patients with a small ventricular septal defect can show changes in the Qp/Qs and document spontaneous closure.

When diagnosis of a large ventricular septal defect is suspected cardiac catheterization is necessary to obtain precise anatomic definition and to measure pulmonary arterial pressure and pulmonary vascular resistance. Therefore, radionuclide angiography is unnecessary.

A decrease in shunt flow in patients with a large ventricular septal defect could be secondary to spontaneous closure of such a defect, the development of pulmonary stenosis or to increased pulmonary vascular resistance. If the latter is considered a possibility, cardiac catheterization is needed. In this situation a thallium-201 scintigram at rest will show increased uptake of this radionuclide in the right ventricular myocardium due to right ventricular hypertrophy.[54–56] The degree of right ventricular uptake of thallium-201 relates to the degree of right ventricular hypertension.

In both immediate and long-term postoperative periods, radionuclide angiography can be used to evaluate residual shunts or palliative shunts (Table II). Mobile equipment permits radionuclide angiography to be performed in intensive care units.

Evaluation of ventricular function and therapy: The gated blood pool scan is useful in evaluation of ventricular function and the effect of therapy. The echocardiogram is difficult to interpret in patients with cystic fibrosis because of their increased lung volume. When they have clinical evidence of right heart failure, gated blood pool scans allow quantitation of right heart function (Fig. 6). Left and right ventricular function can also be evaluated with gated blood pool scans in patients with primary or secondary cardiomyopathy, such as that due to thalassemia and adriamycin toxicity.

Measurement of regurgitant index: Gated blood pool studies can be used to measure regurgitant index by dividing the left by the right ventricular stroke volume.[57] The determination of regurgitant index can help localize an intracardiac shunt. For example, in atrial septal defect, only the right ventricle exhibits volume overload, whereas both ventricles exhibit volume overload in ventricular septal defects.

Thallium-201 can assist in the definition of the nature of cardiac tumors, but these are best detected with radiography and echocardiography.

Myocardial infarct imaging: Infarct imaging is used frequently in adult patients.[58] In children, infarct imaging is useful after cardiovascular surgery when the risk for myocardial infarction is great and the diagnostic reliability of electrocardiographic and serum enzyme changes may be low (Table II). The radiopharmaceutical used most commonly for imaging of acute myocardial infarction is technetium-99m pyrophosphate, a bone seeker that has been found to concentrate in infarcts of the brain, heart, spleen and intestine.

Comment

Radionuclide angiography versus echocardiography: During the evaluation of patients with congenital heart disease the pediatric cardiologist may consider the use of radionuclide angiography or echocardiogra-

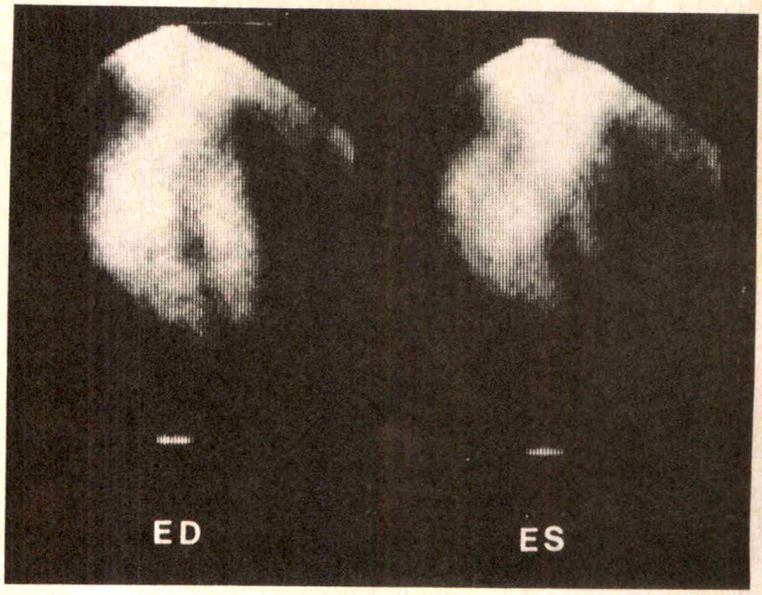


FIGURE 6. Ventricular function in impaired right ventricular function in cystic fibrosis. End-diastolic (ED) and end-systolic (ES) frames in the left anterior oblique projection from a gated blood pool scan obtained in a 27 year old man with advanced cystic fibrosis. The left ventricle contracts well (ejection fraction 0.67) whereas there is definite right ventricular dysfunction (ejection fraction 0.27).

phy. The question may arise: Which study should be performed? Trying to answer this question in one or two sentences would result in a gross oversimplification of the problems that are presented in practice. Improvements in technology continuously expand and refine both methods. It is important for pediatric cardiologists to learn about the advantages and limitations of both techniques. Both are visual, easy to perform and quantitative. Echocardiography provides more excellent anatomic definition whereas radionuclide angiography provides more excellent physiologic information. The use of echocardiography by pediatric cardiologists has increased extensively in the past few years; at present not enough pediatric hospitals have adequate equipment to perform radionuclide angiography. The selection of one or both of these tests should be made on the basis of which information is most desired. Echocardiography and radionuclide angiography should be regarded as complementary noninvasive modalities.

Radiation exposure with radionuclide angiography: Many pediatric cardiologists are concerned regarding the radiation exposure to the patient from radionuclide angiography. Radionuclide studies of the circulation result in low radiation exposure that is well within the range of common radiodiagnostic procedures. It is far less than radiation exposure that occurs with catheterization and angiography. If the diagnostic question could be solved by using a combination of echocardiography and radionuclide imaging the radiation exposure to patients would be significantly reduced. This becomes even more important for children and other patients who need serial follow-up studies.

Newer radiopharmaceuticals for angiography with a very short physical half-life such as iridium-191m (physical half life = 5 seconds) result in a further reduction in radiation dose to the patient. For example, the intravenous injection of 25 millicuries of iridium-191m in a 1 year old results in a radiation exposure of 3 mrad. This is even less than that for a single chest X-ray film. Iridium-191m is being used experimentally in our laboratory and it is hoped that in the next few years there will be more widespread use of this radionuclide for angiography.

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Doppler Echocardiography: Applications, Limitations and Future Directions

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On the basis of principles that are similar to (but differ slightly from) those that underlie M mode and two dimensional techniques, pulsed Doppler echocardiography permits evaluation of intracardiac blood flow noninvasively. This technique is helpful in the diagnosis and management of patients with valvular and congenital heart disease, and in some circumstances provides information not available from M mode or two dimensional imaging. Despite several notable limitations, pulsed Doppler echocardiography is a useful diagnostic technique whose clinical application is likely to increase as future technologic improvements occur.

Cardiac catheterization and contrast angiography permit demonstration of patterns of blood flow within the heart and quantitation of both forward and regurgitant flow. Although these invasive techniques provide the standard method for studying disturbances of intracardiac blood flow in the clinical setting, they generally require hospitalization and are relatively expensive, associated with known complications and not well suited for repeated studies. The noninvasive technique of pulsed Doppler echocardiography offers an alternate method for investigating intracardiac blood flow.[1–3]

Principles

The Doppler principle states that the frequency of transmitted sound is altered (or "shifted") when the sound source is moving. This principle can be used to detect intracardiac blood flow, because blood contains particles (predominantly red cells) that reflect or scatter ultrasound and thus can be considered as a sound "source." As the red cells flow through the heart and great vessels, they alter the frequency of sound backscattered from their surfaces; these frequency shifts can be used to define the direction and nature of blood flow.[3] For example, consider a beam of ultrasound directed down the ascending aorta from a transducer placed in the suprasternal notch (Fig. 1). During systole, red cells are ejected toward the transducer into the aortic root (panel A). According to the Doppler principle, the frequency of the backscattered sound will be increased (compared with the original emitted frequency). If aortic insufficiency were present, blood would flow from the aortic root into the left ventricle during diastole; signals backscattered from red cells flowing away from the transducer would have a lower frequency than that of the incident beam. Because only the component of velocity that acts along the axis of the beam is detected, red cells moving at right angles to the axis of the ultrasonic beam would cause no Doppler shift.

When blood flow through a cardiac chamber, valve orifice or great vessel is laminar, red cells move in a generally parallel fashion (Fig. 1A). Although flow velocity may be somewhat lower near the walls of the structure than near the center line of flow, adjacent red cells will have similar velocities, and the Doppler frequency shifts induced by these moving red cells will have a fairly uniform character. In contrast, red cells do not move in a generally parallel fashion when intracardiac blood flow is disturbed, as occurs in the presence of a stenotic valve (Fig. 1B). Within the "jet" or region of disturbed flow, red cells will move in varying directions and with varying velocities, and the corresponding Doppler shifts will be composed of multiple, widely fluctuating frequencies.

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To specify the intracardiac location from which Doppler shifts are recorded, the pulsed Doppler instrument utilizes a "range-gate," a brief "window" during which flow signals are evaluated. The time delay between emission of an ultrasonic burst and the beginning of the "window" is adjustable, and determines the depth (in relation to the transducer) at which flow is studied. Flow signals are thus recorded from a region known as the "sample volume" that has a teardrop shape and measures approximately 3 to 4 mm in length by 2 to 5 mm in width, depending on the position of the sample volume along the axis of the ultrasonic beam. The location of the sample volume is adjusted in relation to accompanying echo signals reflected from the acoustic interfaces traversed by the ultrasonic beam.

Flow signals are processed to provide both audio and graphic outputs.[4] Audio signals correspond to the spectrum of Doppler shifts produced by moving red cells; laminar flow induces uniform frequency shifts and thus sounds tonal and "smooth," whereas disturbed flow causes a broad spectrum of frequency shifts and thus sounds noisy and "rough." Characteristic sounds generated by flowing blood or by motion of valve leaflets and cardiac walls into the region of the sample volume help the experienced examiner to position the sample volume for recording.

The graphic output generates a time interval histogram, a pattern of dots printed on strip chart paper that denotes the direction (toward or away from the transducer) and nature (laminar or disturbed) of blood flow. A detailed description of the graphic display system can be found in an earlier work from our laboratory.[4]

Findings

Pulsed Doppler echocardiography has a variety of clinical applications, including detection of valve stenosis and insufficiency, identification of subvalve or supravalve stenoses, detection of shunt lesions (including atrial and ventricular septal defect as well as patent ductus arteriosus) and identification of the origin of clinically detected murmurs.[2,5–15] Although it is not practical to illustrate the findings in all of these abnormalities, several representative examples follow.

Valve Stenosis and Regurgitation

Aortic valve disease: With the transducer held at a high parasternal position, left ventricular outflow in a normal person is recorded as a narrow band pattern of dots that indicates flow toward the transducer (Fig. 2A). No evidence for diastolic regurgitant flow is recorded. In a patient with thickened aortic leaflets and some associated disturbance of left ventricular outflow (Fig. 2B), the graphic display shows systolic dot scatter, indicating spectral broadening. Diastolic flow is not recorded. In the presence of aortic regurgitation (Fig. 2C), diastolic flow from the aortic root into the left ventricular outflow tract, directed away from the transducer, is detected. Note that valve regurgitation can be defined by recording retrograde flow through a cardiac valve at a time in the cardiac cycle when such flow should not occur (in this example, detection of diastolic flow from the aortic root into the left ventricular outflow tract). Although absolute flow velocities in the setting of valve regurgitation are generally not as high as those that accompany valve stenosis with "jet" flow, audible and graphic evidence of spectral broadening often accompanies regurgitant flow, indicating that the *nature* (as well as the *direction* and *timing*) of regurgitant flow is abnormal.

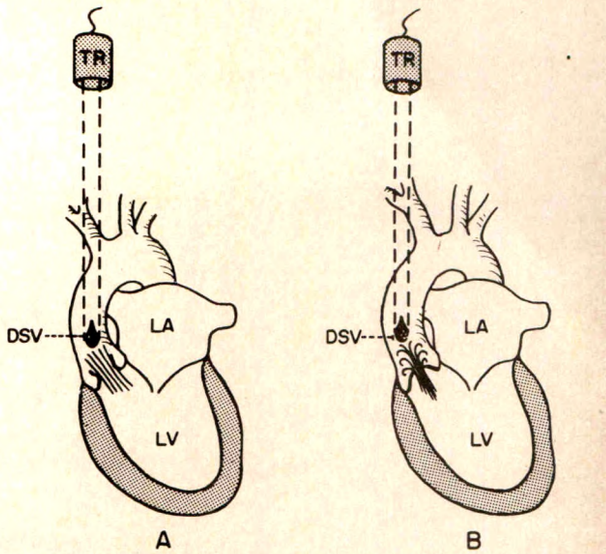


FIGURE 1. Diagrammatic representation of the heart in frontal view. The ultrasonic transducer (TR) is located in the suprasternal notch, and the ultrasonic beam directed inferiorly. The Doppler sample volume (DSV) is positioned in the ascending aorta. **A,** normal (laminar) left ventricular (LV) outflow. **B,** aortic stenosis with disturbed left ventricular outflow. LA = left atrium.

Mitral valve disease: With use of the precordial approach, flow patterns can also be recorded from the left atrial outflow tract, just proximal to the mitral orifice. In a normal subject (Fig. 3A), diastolic flow from the left atrium into the left ventricle is directed toward the transducer, and causes an upward deflection of the dot pattern in the time interval histogram. An early diastolic flow peak is followed by a period of diastasis, which mirrors the anterior mitral leaflet echogram; atrial contraction causes a small increment in atrial outflow. During systole, no flow signals from the left ventricle into the left atrium are recorded. Although systolic pulmonary venous inflow into the left atrium is occasionally detected using the audio output, this is extremely difficult to record graphically (perhaps because this flow is of relatively low velocity and is sampled at great depth). In a patient with mitral stenosis (Fig. 3B), diastolic left ventricular inflow is prolonged (signals continue through diastole), and the wide band pattern of dots indicates that flow through the stenotic mitral orifice is disturbed. In the presence of mitral regurgitation (Fig. 3C), disturbed systolic flow from the left ventricle into the left atrium (away from the transducer) is recorded.

Accuracy of method: In our experience, pulsed Doppler echocardiography can detect the presence of aortic insufficiency with 86 percent sensitivity and 93

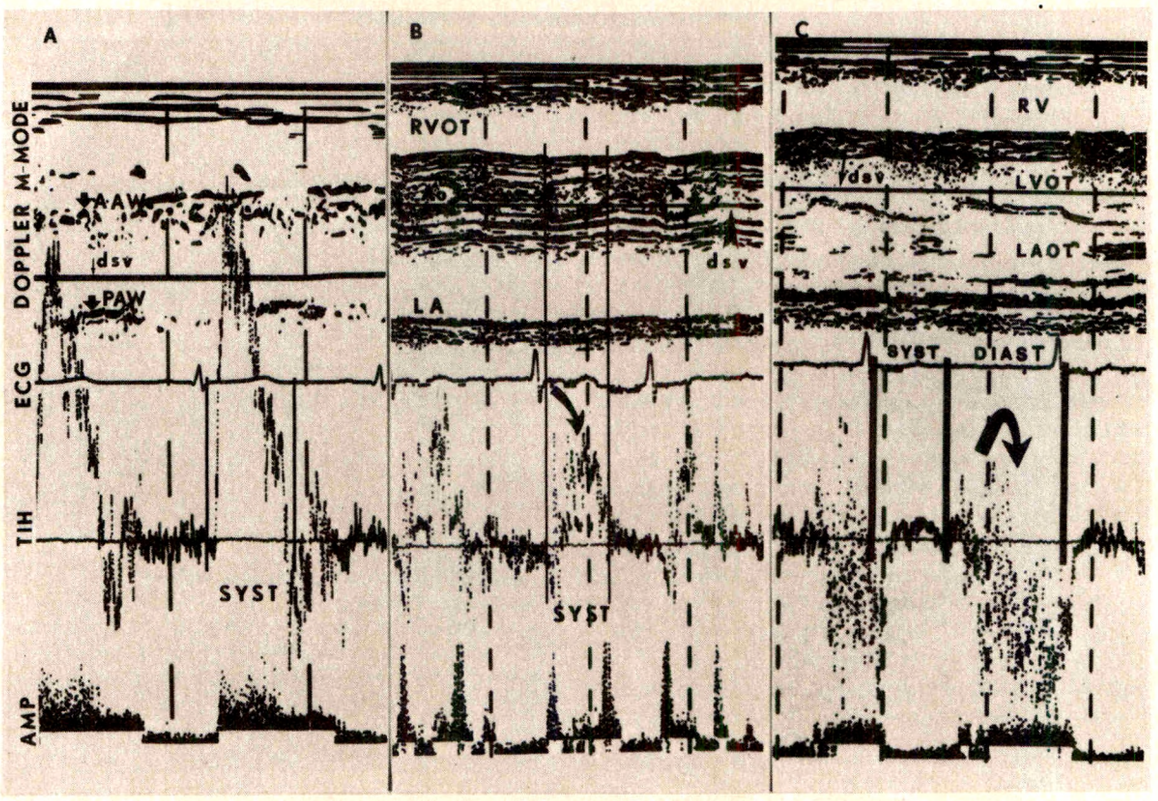


FIGURE 2. Strip chart Doppler flow records obtained using the precordial approach. At the top of each panel, a condensed M mode tracing is displayed. A horizontal straight line, recorded with this tracing, indicates the position of the Doppler sample volume (dsv). The time interval histogram (TIH) reflects the Doppler shifts and indicates flow. By convention, deflection of dots above the baseline indicates an increase in flow velocity and denotes blood flow toward the Doppler transducer; flow away from the transducer is indicated by deflection of the dots below the baseline. Laminar flow is denoted by a narrow band of dots and disturbed flow by a broad band of dots. At the bottom of each panel, spikes whose amplitude (AMP) denotes the intensity of the Doppler signals are recorded; these help in setting instrument gain and threshold. **A,** normal left ventricular outflow; the sample volume is positioned in the aorta just above the valve leaflets. **B,** disturbed left ventricular outflow; the sample volume lies in the aorta (Ao) in the region of the thickened valve leaflets (**short arrows**). The **curved arrow** indicates systolic (SYST) dot scatter in the time interval histogram, denoting spectral broadening in the Doppler shift signals. **C,** aortic regurgitation; the sample volume lies just proximal to the aortic leaflets in the left ventricular outflow tract (LVOT). The **curved arrow** indicates diastolic (DIAST) dot scatter below the baseline, denoting disturbed diastolic regurgitant flow. AAW = anterior aortic wall; LAOT = left atrial outflow tract; PAW = posterior aortic wall; RV = right ventricle; RVOT = right ventricular outflow tract; other abbreviations as in Figure 1.

percent specificity[6]; for mitral insufficiency, sensitivity is 95 percent and specificity 90 percent.[7] Although these earlier studies included only 157 patients, our continuing clinical experience supports the position that the pulsed Doppler technique is quite accurate in detecting the *presence* of valve insufficiency; two more recent studies of patients with suspected mitral regurgitation have reported results nearly identical to our own.[16,17] Moreover, preliminary studies suggest that the *severity* of valve insufficiency can also be estimated by pulsed Doppler echocardiography; when widespread Doppler evidence for abnormal flow is present, cineangiographic valve regurgitation is generally severe, whereas milder grades of regurgitation are accompanied by only localized Doppler evidence of disturbed flow.[14,16]

Intracardiac Shunts

Ventricular septal defect: The diagnosis of intracardiac shunting is greatly facilitated by pulsed Doppler echocardiography. Patients with an atrial or ventricular septal defect and those with patent ductus arteriosus often demonstrate anatomic abnormalities detectable with conventional echocardiography, but these findings are nonspecific. However, the presence and level of left to right intracardiac shunting can be defined by recording turbulence distal to the lesion in question (that is, on the right heart side of the defect), and by then "threading" the defect with the sample volume to demonstrate the presence of flow *within* the defect itself. Thus, in a patient with a ventricular septal defect (Fig. 4, top), disturbed flow can be recorded with the sample volume in the right ventricular outflow tract. Because similarly disturbed right ventricular outflow could be caused by subpulmonary stenosis, this finding would not be diagnostic of ventricular septal defect. However, transducer angulation can be adjusted so as to scan the sample volume along the right septal surface, thereby defining the level at which abnormal flow signals are most easily recorded. At that point, the sample volume is advanced away from the transducer and "threaded" through the defect. Recording of abnormal systolic flow signals with the sample volume positioned *in* the ventricular septum confirms the diagnosis of

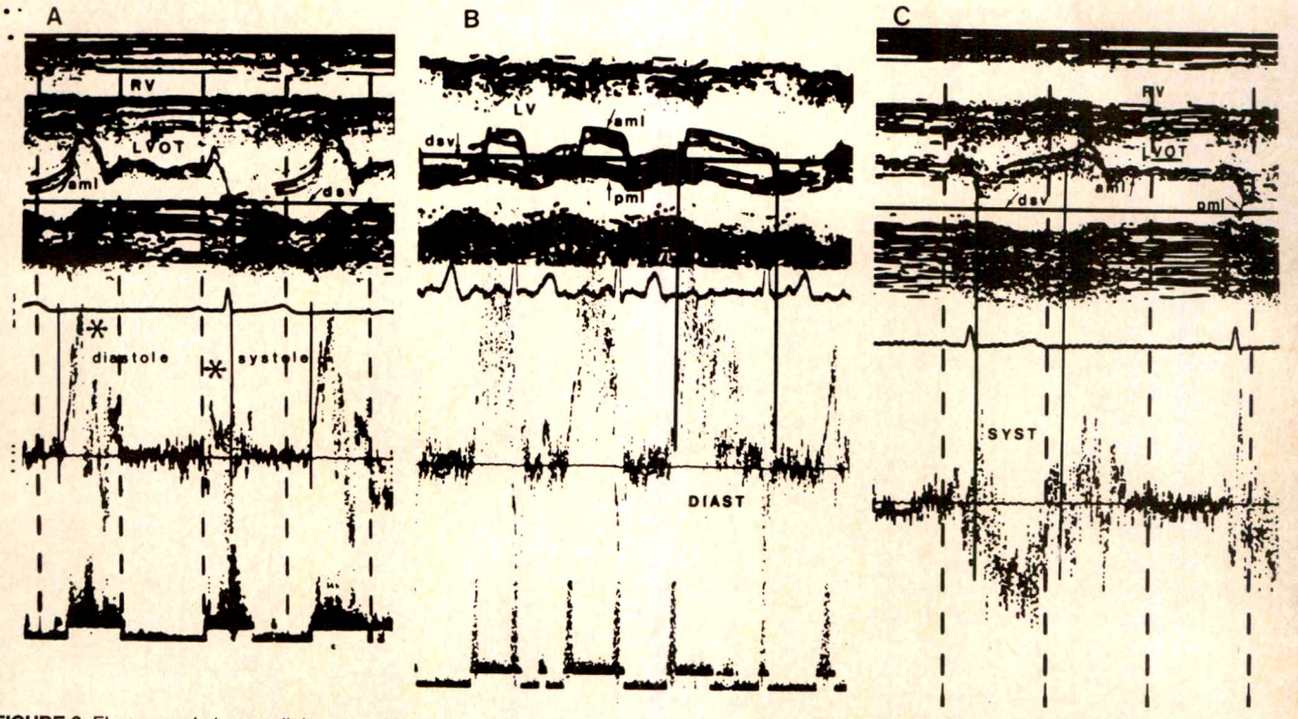


FIGURE 3. Flow records (precordial approach) obtained with the sample volume in the left atrial outflow tract; same format as in Figure 2. **A,** normal subject; the asterisks indicate left ventricular inflow during early and late diastole. **B,** mitral stenosis. **C,** mitral regurgitation. aml = anterior mitral leaflet; pml = posterior mitral leaflet; others as in Figures 1 and 2.

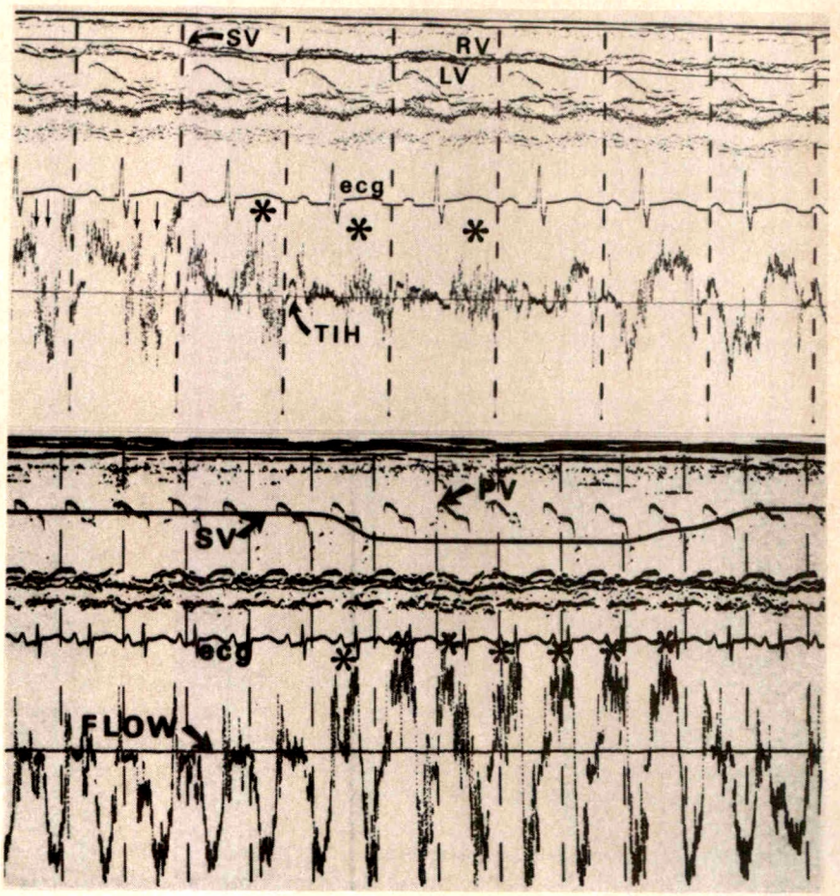


FIGURE 4. Intracardiac shunts. **Top,** ventricular septal defect. On the left of the panel, the sample volume is in the right ventricular (RV) outflow tract. The time interval histogram (TIH) shows systolic dot scatter (**thin arrows**). As the sample volume is advanced into the ventricular septum, disturbed systolic flow signals persist (**asterisks**). On the right side of the panel, systolic flow towards the transducer is recorded in the left ventricle (LV). **Bottom,** patent ductus arteriosus. On the left side of the panel, the sample volume (SV) is proximal to the pulmonary valve (PV). Systolic flow signals are normal, while no diastolic signals are recorded. As the sample volume is advanced beyond the pulmonary valve, disturbed diastolic flow towards the transducer is recorded (**asterisks**), indicating flow from the aorta into the pulmonary artery. Abbreviations as in Figures 1 and 2.

ventricular septal defect. In our experience, this defect can be detected by conventional pulsed Doppler technique with a sensitivity of approximately 90 percent and a specificity of approximately 98 percent.[12] Low muscular septal defects can be detected, but their location and orientation often make them difficult to "thread."

Patent ductus arteriosus: This shunt can be detected quite easily from the parasternal examining window (Fig. 4, bottom). Systolic right ventricular outflow is recorded as a narrow band dot pattern below the baseline (indicating flow away from the transducer). However, when the sample volume is advanced beyond the valve into the pulmonary artery, abnormal diastolic flow into the main pulmonary artery (from the aorta through the ductus) is recorded, indicating left to right shunting at this level. In our experience, patent ductus arteriosus accompanied by left to right flow can be detected with over 90 percent sensitivity and nearly 100 percent specificity.[15] Moreover, the presence or absence of associated pulmonary hypertension can be deduced from the duration of abnormal flow during diastole.[13]

Limitations

Time interval histogram: A number of limitations in conventional pulsed Doppler instrumentation should be noted. The time interval histogram imposes several major limitations. This display plots the inverse of the intervals between successive zero crossings in the Doppler shift signal against time. However, because the Doppler signal is not a perfect sine wave, its frequency content cannot be reflected accurately by the zero crossing detector. Moreover, the time interval histogram is gain- and threshold-dependent, and its output is thus difficult to calibrate. The relatively low signal-noise ratio of the detected Doppler signal creates additional problems; when high gain and low threshold settings are necessitated by the presence of weak Doppler signals, electronic "noise" inherent in the instrument itself may cause the graphic display to print a wide-band dot pattern, even in the presence of normal intracardiac blood flow. Such apparent spectral broadening might mistakenly be interpreted as indicative of disturbed blood flow.

Audio output versus graphic output: Characteristics of the audio signal are less influenced by gain and threshold settings, and we have found diagnostically useful information in the audio output even when the time interval histogram is technically inadequate. For these reasons, the audio output often must supplant the graphic output as the primary diagnostic modality, particularly in adult patients. Although this method has provided information about valve lesions and intracardiac shunts often not available with other noninvasive techniques, analysis of the Doppler audio output is undeniably subjective, nonquantitative and difficult to demonstrate. It is noteworthy that use of the stethoscope to auscult the heart is also subjective, nonquantitative and difficult to demonstrate, but nonetheless remains a useful diagnostic technique.

Rate of sampling: pulse repetition frequency: Sampling theory dictates that one must sample a multifrequency signal at no less than twice the highest frequency present in order to characterize accurately all of the frequency components of the spectrum. The rate of sampling in the Doppler instrument, the rate at which bursts of ultrasound are emitted by the transducer, is called the "pulse repetition frequency." The pulse repetition frequency is inversely related to the distance between the transducer and the intracardiac position of the sample volume[3]; the farther the sample volume from the transducer, the lower the pulse repetition frequency. Thus, high frequency components of flow velocity (often present in the setting of valve stenosis and ventricular septal defect) may be difficult to detect, particularly when high velocity flow is oriented parallel to the axis of the ultrasonic beam and occurs at an intracardiac location distant from the transducer. When Doppler shift frequencies exceed half the pulse repetition frequency, "foldover" of the dot pattern toward the baseline occurs in the time interval histogram output. This is referred to as "aliasing," and might potentially be confused with the pattern of dot scatter (true spectral broadening) seen in disturbed flow.

Precordial versus cardiac apical approach: Pulsed Doppler studies are generally performed using the left precordial approach in order that the motion pattern of accompanying echoes can be recognized and used to position the sample volume. However, transmission of ultrasound from the precordium is poor in certain patients, making an adequate Doppler examination impossible. Moreover, because the axis of blood flow into and out of the left ventricle is oriented at nearly 90° to the incident ultrasonic beam directed from the precordium, Doppler shift signals may be difficult to record even if flow velocities are substantial. Both of these limitations could be overcome by placing the transducer at the cardiac apex. However, M mode echoes recorded from the apical window are difficult to identify, so that positioning of the sample volume would need to be based on directional flow characteristics and audio output evidence of valve opening and closing sounds.

Single range gate and single sample volume: Current Doppler systems use only a single range gate and thus allow examination of blood flow at only one intracardiac location at a time. If disturbed flow is directed unusually, it may be "missed" by the sample volume; for example, eccentric "jets" of mitral regurgitation located just behind the posterior aortic wall have occasionally gone undetected by sampling in the mitral orifice or left atrial cavity.[7] Moreover, the availability of a single sample volume limits "mapping" of the spatial distribution of disturbed intracardiac flow (in order to evaluate the severity of the flow disturbance). This technique is based on the assumption that the geometry of disturbed flow is consistent from beat to beat. Unfortunately, arrhythmias and alterations in loading conditions probably do affect the spatial distribution of flow disturbances and invalidate the foregoing assumption.

Quantitation of flow velocity and volume flow: Because of many of the preceding limitations, current pulsed Doppler techniques do not allow quantitation

of actual flow velocity or volume flow. The audio and graphic outputs can only be calibrated to measure that component of flow velocity directed along the sound beam axis. Calculation of actual volume flow would require measurement of the average velocity of blood flow as well as the cross-sectional orifice through which flow occurs. Two dimensional echocardiography could define the cross-sectional flow "orifice" of a cardiac chamber, valve or vessel. However, measurement of average flow velocity would require knowledge of the angle between the ultrasonic beam and the axis of blood flow, as well as the profile of Doppler shifts across the flow orifice. Neither of these latter variables is directly available using current Doppler instrumentation.

Anticipated Improvements

Computer techniques: The need for an objective, sensitive method for Doppler signal analysis has been emphasized. Several groups have applied computer techniques for spectral analysis of Doppler signals,[18,19] and this approach appears to offer improvement over the time interval histogram method. Unfortunately, standard computer techniques are somewhat cumbersome and expensive, and probably are not practical for general clinical application. The use of new digital technology for true frequency analysis of Doppler shift signals is being investigated, and appears promising.

Combined Doppler/two dimensional echo systems: Pulsed Doppler and two dimensional echocardiography have been combined in several prototype and commercial devices and used to investigate peripheral vascular, pediatric and adult cardiac disease. Most of these devices utilize a mechanical sector scanner; because motion of the piezoelectric crystals would induce artifactual Doppler shifts, these instruments do not allow simultaneous recording of Doppler signals and real time images. However, the combination of pulsed Doppler with two dimensional echocardiography does permit examination of cardiovascular structures from multiple echo windows, positioning and orientation of the sample volume in relation to spatially recognizable structures, and more favorable alignment of the ultrasonic beam with the axis of blood flow. This technique holds promise for increasing the number of patients in whom Doppler studies can be performed. Moreover, preliminary work suggests that combined Doppler/two dimensional echo systems may be used to detect the presence and study the spatial distribution of disturbed flow in patients with valve insufficiency[20,21] and septal defects.

Cardiac tracking device: Two other useful modifications have been reported recently.[19] A sample volume whose size can be varied along the sound axis permits examination of average Doppler shifts across the entire diameter of a cardiac structure (for example, the aortic root or mitral orifice). A cardiac tracking device has been developed to permit the sample volume to follow the motion of a cardiac structure; this has been helpful in deriving an index of flow velocity through stenotic mitral valves. Similar approaches should help make Doppler techniques more quantitative, and thus more useful for assessing the severity of various flow disturbances.

Multigate Doppler technique to examine flow signals at multiple locations: While the preceding modifications increase the level of sophistication of Doppler signal acquisition and analysis, they are all limited to investigating flow in the region of a single sample volume. A prototype multigate, digital Doppler instrument, constructed recently in our laboratory, permits simultaneous examination of flow signals at multiple locations.[22] Currently, this system utilizes a single crystal transducer; echo and Doppler shift signals are detected coherently and processed simultaneously at up to 128 sites. A time-motion tracing can be recorded by sweeping the echo and Doppler signals across an oscilloscopic screen; anatomic features are depicted in grey scale, while flow features are superimposed and displayed in color. The multigated Doppler technique thus provides a recording that is relatively easy to understand, and translates flow abnormalities into an anatomic form of display. Our initial experience indicates the utility of this technique in detecting a variety of valve lesions and intracardiac shunts[22,23]; further studies will be needed to define the degree to which this technique may supplant conventional Doppler methods. Finally, it should be noted that a multigated processor for coherent echo/Doppler detection could be applied to real time imaging in order to provide two dimensional images of flow through the beating heart.

Current Indications

Pulsed Doppler echocardiographic studies should be considered when the integrity of cardiac valve function or the possibility of an intracardiac or extracardiac shunt requires evaluation. In these instances, diagnostic information not available from clinical or other noninvasive tests may be obtained. Likewise, the origin of clinically apparent murmurs may be detected. In patients with valve stenosis, pulsed Doppler findings complement the anatomic findings, but are probably of secondary importance. The use of the Doppler technique for this application and for determining ventricular stroke volume is likely to increase in the future as more quantitative methods are developed.

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Evaluation of Ischemic Heart Disease With a Prototype Volume Imaging Computed Tomographic (CT) Scanner: Preliminary Experiments

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A prototype synchronous volumetric computed tomographic X-ray scanner was used to demonstrate, in individual experiments, the possibility of estimating percent coronary arterial stenosis, regional myocardial blood supply and regional myocardial wall dynamics. Scans were obtained during angiography in intact anesthetized dogs or in an isolated metabolically supported working left ventricular preparation. Percent arterial stenosis was quantitated using the percent change in brightness area product of successive cross-sectional images of contrast agent-filled Tygon® tubing sutured to the epicardium. Myocardial blood supply was evaluated by the transmural and circumferential extent and the time rate of change of myocardial opacification during coronary angiography. The regional time rate of change of left ventricular wall thickening during the systolic phase of the cardiac cycle was demonstrated in the isolated ventricle preparation. The recently installed Dynamic Spatial Reconstructor high speed volumetric scanning system will be used to make these measurements from scan data obtained during a single angiogram in man.

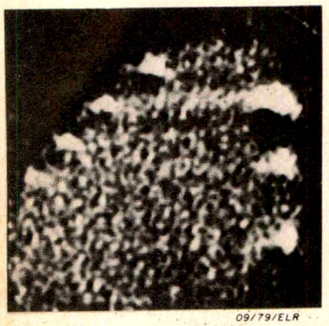
Among the distinctive features of ischemic heart disease are localized stenosis of coronary arteries, variable extent and magnitude of collateral blood supply to the myocardium and reduced functional reserve of myocardial regions. The disease decreases global cardiac function to a degree that depends on the amount of total myocardium affected and, to some extent, on the location of the affected area. Most diagnostic techniques quantitate only one aspect of the multiple manifestations of the disease process with fairly good sensitivity. However, these techniques generally cannot, in themselves, provide a measure of the relative importance of the particular manifestation studied. For instance, high quality coronary arteriography may demonstrate the presence of coronary collateral flow or of severe coronary arterial stenosis, yet the physiologic importance of these features in the patient under study can be deduced only indirectly from that angiogram. As a consequence, multiple independent tests are commonly used to provide independent measures of all the manifestations of the disease process. Because these tests are generally performed at different times and under different physiologic conditions the relative importance of these various manifestations generally remains open to question.

The dynamic spatial reconstructor (*DSR*), a multiple X-ray source (computed tomographic [CT]) scanner, has recently been installed and is currently undergoing preliminary test procedures.[1] This device has four operational characteristics that permit simultaneous estimation

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COMPUTER-GENERATED DISPLAYS OF "CT" IMAGE OF HEART
(310 mg I_2/ml Renovist in Tygon Tubing)



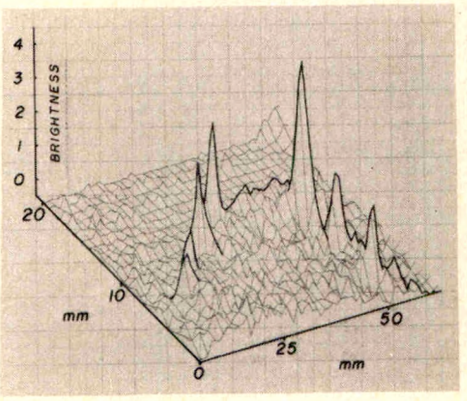


FIGURE 1. Left, transverse section image (1 mm thick) of the region of the heart. The elliptical gray zone is the section of the heart surrounded by heart tissue. Bright spots correspond to contrast medium (310 mg iodine/ml) in the tube lumens. **Right,** perspective plot of the computed tomographic (CT) image in the **left panel.** The vertical (Z) axis represents the brightness of the computed tomographic image shown in the **left panel.** The peak deflections represent the contrast agent-filled Tygon tubes.

of global cardiac function, coronary anatomy and regional myocardial perfusion and function throughout the myocardium. These characteristics are: (1) reconstruction imaging of a volume large enough to encompass the entire heart, (2) synchronous imaging of this volume, (3) stop action imaging of this volume, and (4) rapid repetition imaging of this volume. Experimental evidence that this imaging approach is technically feasible has been described in detail elsewhere.[2] This paper illustrates use of a prototype[3] of the electronic scanning dynamic reconstruction system to demonstrate that multiple manifestations of ischemic heart disease can be quantitated relatively noninvasively.

Methods

Four aspects of ischemic heart disease that can be quantitated with the dynamic spatial reconstructor simultaneously were studied independently in different dogs. The basic scanning technique used in all cases is described in detail elsewhere.[2] The scans generate 240 images of 1 mm thick adjacent transverse sections encompassing the entire heart. Scanning of this stack of sections is repeated 60 times/s.

Coronary arterial "anatomy": A 15 kg dog was anesthetized and Tygon tubes of various diameters were sutured to the epicardium after mid sternal thoracotomy. Three scans were performed, one with full strength roentgen contrast agent (310 mg iodine/ml) in the Tygon tubing, one with half strength contrast agent, and finally one with quarter strength contrast agent. Transverse sectional images of the heart were analyzed as follows:

1. *Locations of the contrast agent-filled tubes were identified in each of the transverse images and the cross-sectional area of the tube was measured.* The outline of the contrast agent-filled lumens was taken to be that region of the image where the brightness (that is, CT number) exceeded the mean brightness (+2 standard deviations of the variability) for the adjacent heart wall.

2. *The product of the brightness and area was also calculated for each tube.* This value consists of the sum of the computed tomographic values (that is, tube CT number minus heart wall CT number) for all pixels within the image of each lumen.

Transmural blood volume dynamics: A 14 kg dog was anesthetized and two atrial transseptal catheters were positioned with their tips in the left atrium. The heart was paced with a right atrial bipolar pacing catheter. During the scanning, contrast agent (310 mg iodine/ml solution) was infused continuously at a rate of 1 cc/s into the left atrium. Computed tomographic (CT) values in the subendocardial third, mid wall third and subepicardial third of the left ventricular free wall were "sampled" in each 0.033 second image throughout the cardiac cycle.

Reduced perfusion of the region of myocardium supplied by a ligated coronary artery: A 16 kg dog was anesthetized and the chest opened by means of a left thoracotomy. The left anterior descending coronary artery was ligated about halfway between its origin and the apex of the left ventricle. Both vagal nerves were exposed in the neck and stimulating electrodes attached. During the scan, the dog was rotated continuously with ventilation suspended and cardiac asystole maintained by continuous vagal stimulation. During the rotation, contrast agent was infused continuously into the aortic root through a catheter at a rate of about 2 cc/s.

Regional and global myocardial function: A 15 kg dog was anesthetized and a thoracotomy performed. The left common coronary artery was cannulated with arterial blood from a larger heparinized donor dog. The major vessels of the heart were ligated and divided. The aorta and left atrium were cannulated and attached to a circuit. The right ventricle and atrial free walls were resected. The isolated heart preparation was suspended from the aorta and the entire preparation could be rotated for a scan. The circuit from the aorta to the left atrium contained radiopaque contrast medium (45 mg iodine/ml), and the left atrial pressure and aortic outflow resistance were controlled. This preparation maintained cardiac output and pressures comparable with those expected for a denervated ventricle of similar size in the intact dog. With this preparation, stroke output could be independently measured by a direct volumetric method on a stroke to stroke basis. After a scan was performed under control conditions, the left circumflex coronary artery was ligated 2 cm distal to its origin and the scan repeated.

Results

Coronary arterial anatomy: A single "zoom" reconstruction of the region of the heart is shown in the left panel of Figure 1. The contrast agent in the epicardial tubes shows as bright spots whose size depends on the internal diameter

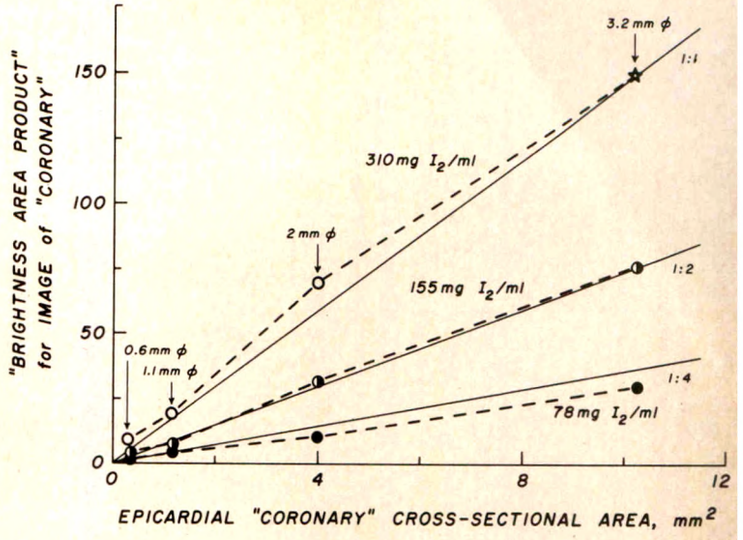


FIGURE 2. Brightness-area product (see text) of imaged Tygon tubes filled with contrast agent correlates well with relative cross-sectional area of the tubing with diameters ranging from 0.6 to 3.2 mm. Note maintenance of the 4:2:1 ratio of brightness-area product values for the 100, 50, and 25 percent concentrations of contrast agent in the tubes. The data were obtained from a 15 kg dog with Tygon tubing sutured to the epicardium.

of the tubing. Because the concentration of contrast agent is identical in all tubes, the brightness of all tubes should be equal. However, the perspective plot (Fig. 1, right) shows that the brightness of the tubes of small diameter is less than that of the tubes with a larger diameter. In addition, the diameters of the bright areas are larger than would be expected from the true tube diameter. These two blurring effects are attributed to the modulation transfer function characteristics of the imaging process. Figure 2 illustrates the relation between true tube luminal cross-sectional area and the brightness-area product computed from the images. The effect of roentgen contrast agent concentration on the accuracy of estimates of relative tube size is also demonstrated in this figure.

Transmural blood volume dynamics: Because the roentgen contrast medium Renovist® used in these studies remains largely within the intravascular compartment during its first passage through the heart, the increase in radiopacity of myocardium must be proportional to the blood volume content of the intravascular space in the myocardium and the concentration of contrast agent in the blood. Transmural distribution of the myocardial blood volume, as indicated by the distribution of contrast agent in the left ventricular wall, is indicated in Figure 3. The computed tomographic (CT) number, or brightness, of regions of the myocardium should vary in proportion to blood content of the myocardium. During the end-diastolic phase of the cardiac cycle, the sub-

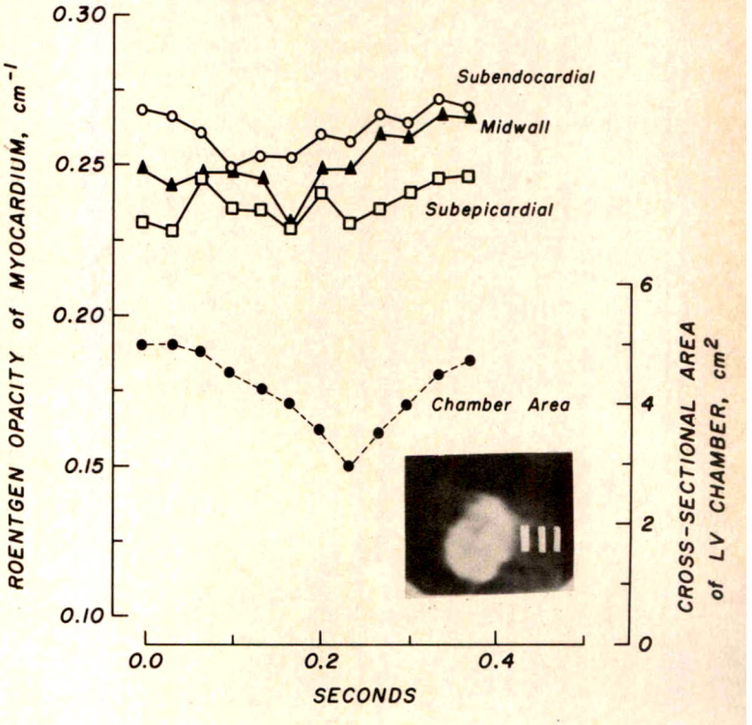


FIGURE 3. The roentgen opacity of a fixed volume of myocardium imaged in a transaxial image (see photographic insert) is sampled at intervals of 1/30th of a second throughout a single averaged cardiac cycle. Roentgen opaque contrast agent (310 mg iodine/ml) infused continuously at rate of 1 ml/s into the left atrium of a 14 kg dog causes a "bright" left ventricular chamber. The three rectangular areas indicate selected subendocardial, mid wall and subepicardial areas for which the average CT number was sampled. The phase of the cardiac cycle is indicated by chamber cross-sectional area plotted in **solid circles.** The dynamic variation of myocardial CT values is plotted for the three selected areas.

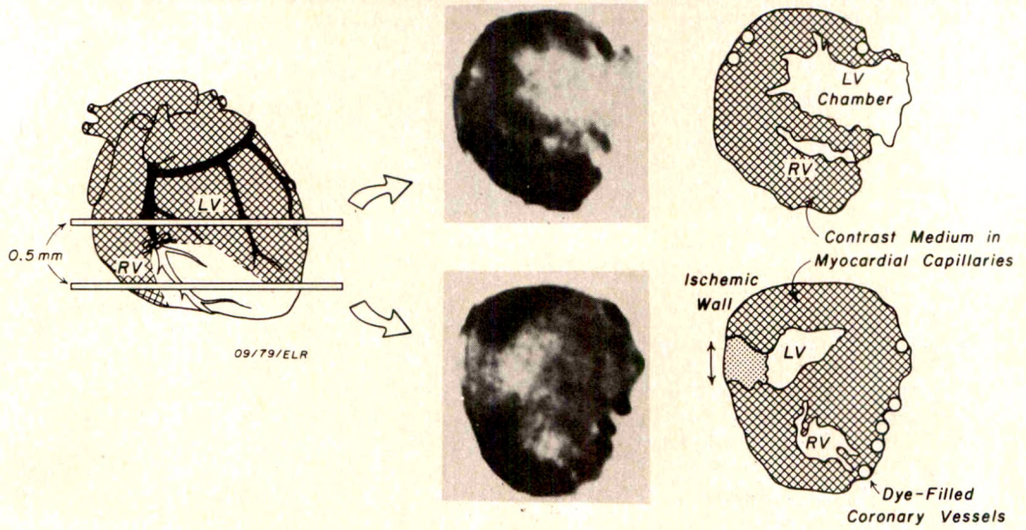


FIGURE 4. Transverse section images of in situ canine heart (at the locations indicated in the left panel) indicate transmural distribution of roentgen contrast agent (that is, blood "content" of myocardium). The gap at "9 o'clock" in the lower image represents the unopacified free left ventricular (LV) wall. RV = right ventricle.

endocardium is more opaque than is the subepicardium, a finding consistent with published data[4] indicating preferentially increased subendocardial blood content in the normal heart. Subendocardial opacity (that is, blood content) decreases more than does subepicardial opacity during the early systolic phase; this observation is consistent with the hypothesis that subendocardial compression squeezes blood out of the subendocardium.

Transmural perfusion deficit distal to ligated coronary artery: Figure 4 illustrates the reduced presence of roentgen contrast agent in the anterior free wall of the left ventricle in the heart of a dog whose left anterior descending coronary artery was ligated before the angiogram and scan were performed. The area of the wall with markedly decreased blood content is quite sharply demarcated and involves the entire wall thickness.

Regional and global myocardial function: The ability of the technique to image the moving wall of the working isolated left ventricle is illustrated in Figure 5. For evaluation of global ventricular function, total left ventricular myocardial mass and chamber volumes were calculated. These calculations were achieved by identifying the endocardial and epicardial surfaces in each transverse image and calculating the area enclosed by each surface. On the basis of the calculated thickness of each transverse slice imaged, the volume of muscle and chamber imaged in each slice was calculated. Total left ventricular wall volume and chamber volumes were calculated merely by adding the respective volumes in all the slices encompassing the apical to basal extent of the left ventricle. This procedure was performed for each 0.0167 second throughout one average cardiac cycle synthesized from the multiple cardiac cycles imaged during the scanning process. Stroke volume was altered by changes in left atrial filling pressure and aortic outflow resistance. The relation of com-

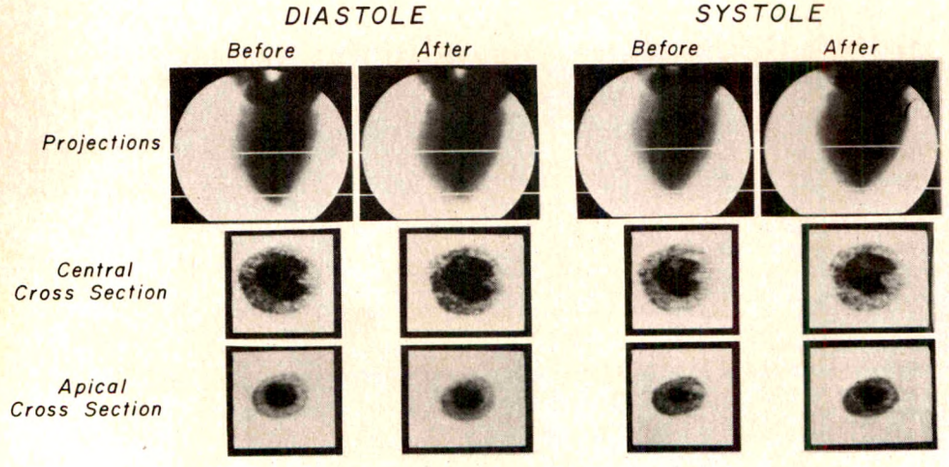


FIGURE 5. X-ray video projection images of a beating isolated canine left ventricle (**top row**) recorded during diastole and systole before and after ligation of the left circumflex coronary artery, and reconstructed cross sections of ventricle (**bottom two rows**) at the two levels indicated by brightened lines, determined for diastole and systole before and after ligation of the circumflex coronary artery. (Reproduced, by permission, from Robb et al.[5])

puted (Y) versus directly measured (X) stroke volume was Y = 1.04X − 0.5; the correlation coefficient (r) was equal to 0.89 over a range of stroke volumes of 4 to 20 cc.

Discussion

Advantages of method: An important feature of the dynamic spatial reconstructor (DSR) approach is that the original scanning data are obtained essentially synchronously within 10 ms, thereby greatly reducing problems related to motion blurring and lack of exact beat to beat reproducibility of shape, dimensions and location of the heart, which would be required for gated computed tomographic scanning. Second, the DSR approach allows retrospective computation of oblique and axial images without degradation of spatial and density resolution. Third, the format of scanning data produced by this approach is such that the thickness of the slice and its exact location and orientation can be positioned retrospectively exactly over the lesion of interest, thereby maximizing the utility of the image. The use of the brightness-area product permits quantitation of relative size of stenoses with diameters much smaller than those it would be possible to quantitate on the basis of objective spatial resolution. The rationale for this index is that the total "energy" incorporated in the cross-sectional image of a small tube filled with contrast agent should remain relatively constant even though it is blurred (that is, spread out) by the imaging process modulation transfer function.

Measurement of relative coronary stenosis: Hemodynamically, the change from an 85 to a 90 percent stenosis may be highly significant in that the resistance to flow increases very rapidly.[6] In a coronary vessel with a diameter of 3 mm this represents a decrease of 0.1 mm in diameter of the vessel. Heroic technologic measures would, at this time, be required to achieve the spatial resolution necessary to quantitate this small change in diameter. Consequently, an accurate measurement of relative stenosis is the best that can be hoped for at present. After all, it is myocardial perfusion that governs the threat to the myocardium so that detection of the presence and location of a stenosis and the determination of an index of its functional severity are important. These capabilities are likely to be adequate for indicating if the stenosis is the probable cause of impaired perfusion.

Measurement of regional transmural blood flow: That regional transmural myocardial blood volume can be measured throughout the cardiac cycle has been demonstrated. Second, the relation between the location of reduced myocardial blood flow caused by an acutely occluded coronary artery and regional wall motion has also been demonstrated. These dynamic and spatial aspects of the passage of contrast agent in blood are the basic variables that need to be measured in order to estimate regional myocardial perfusion. Many of the techniques already well developed for estimation of blood flow with use of roentgen contrast agent injected into the bloodstream support the potential value of this approach.[7] This capability has the exciting potential of providing such quantitative estimates as the relative contribution of collateral perfusion of a region or the presence of subendocardial ischemia as an early index of ischemic heart disease.

Regional wall motion and dynamics: Over the past decade, several clinical studies and animal experiments[8,9] have suggested a direct relation between the magnitude of regional myocardial blood flow and the percent and rate of regional left ventricular myocardial wall thickening during systole and wall thinning during diastole. The data obtained in the working isolated left ventricular preparation are consistent with these data. Moreover, the transaxial image data permit measurement of wall dynamics in all regions of the myocardium. However, the primary potential value of the approach of the dynamic spatial reconstructor (DSR) is that it may permit all of these data to be obtained from a single injection of contrast agent into the right ventricle or pulmonary artery. On the assumption that a concentration of at least 80 mg iodine/ml contrast agent should be present in the aortic root so as to opacify adequately the coronary arteries and myocardium, an injection of at least 0.5 ml/kg is required (Padiyar R, unpublished data). As high speed volume imaging computed tomographic (CT) scan machines like the DSR with higher density resolution become available, perhaps a right atrial or even an intravenous injection of contrast agent might be adequate to achieve these measurements in a single injection.

Acknowledgment

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Regional Myocardial Blood Flow, Metabolism and Function Assessed Noninvasively With Positron Emission Tomography

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Positron emission computed tomography is a new technique of potential value for the noninvasive measurement of myocardial blood flow, mechanical function and, in particular, metabolism. The capability of this new study method is attributable to the technologic innovations of the imaging device and the availability of radioactive tracers that are specific for blood flow and metabolism. The device permits recording of cross-sectional images of the left ventricular myocardium that quantitatively reflect regional tracer tissue concentrations. Use of tracer kinetic models with this new technique permits measurements of regional glucose and fatty acid metabolism of the heart. Positron emission tomography is already an important new tool for investigative studies of cardiac physiology and pathophysiology; its clinical utility remains to be defined.

Among the techniques available for the noninvasive study of the heart, positron emission computed tomography occupies a unique position: It permits assessment not only of regional myocardial blood flow and mechanical function, but also of regional myocardial metabolism. Each aspect of cardiac performance can be evaluated either individually or in combination. It is conceivable that with this new imaging modality the metabolic link between blood flow and mechanical function can be established. Thus, positron emission tomography offers the potential for an improved understanding of global and regional myocardial physiology in health and disease, although it has only recently been used in the field of cardiology. The following discussion is therefore intended to provide a basic understanding of the technical aspects of this new method, to describe approaches that are used for quantitative assessment of cardiac performance and to discuss its potential future use and clinical applications.

Technical Considerations

Autoradiographic nature of the images: There are two reasons for the unique capability of this new imaging modality: (1) the technologic innovations of positron emission computed tomography, and (2) the availability of radioactive-labeled tracers that are specific for metabolic pathways. Technically, positron emission computed tomography overcomes many of the limitations of conventional gamma camera or planar imaging[1–3]. The distribution of radioactive indicators in organs is displayed in a three dimensional fashion. Spatial resolution is depth-independent; that is, structures deep in the body are imaged with the same spatial resolution as those close to the surface. Finally, the effect of varying attenuation of photons as they travel through tissue before reaching the detector can be removed. The design of state-of-the-art positron computed tomographs is similar to that of the present conventional X ray transmission computerized tomographic (CT) scanners.[1] Both techniques use similar algorithms for image reconstruction. However, transmission tomographs use external X rays and determine their attenuation across the body, whereas in positron emission computed tomography the source of radiation resides within the body and its

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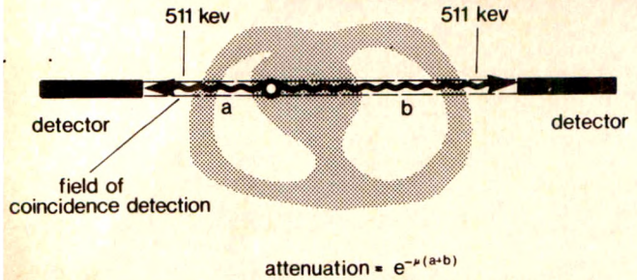


FIGURE 1. Schematic representation of annihilation coincidence detection as the basis of positron emission computed tomography. As the positron interacts with an electron, their combined mass is converted into two 511 keV gamma rays that leave the site of interaction in diametrically opposed directions. The simultaneous emission of the 511 keV gamma rays is detected by a pair of opposing scintillation detectors in coincidence. Interactions only within the field of coincidence detection are recorded. Further, attenuation of the gamma rays by tissue is a function of the path length a and b and the attenuation coefficient (see text).

emissions are recorded for subsequent reconstruction into tomographic images.

Positrons are particles with a mass equal to that of electrons but with a positive charge. As positrons lose their kinetic energy they interact with an electron and are annihilated. Their mass is converted into two 511 keV photons that leave the site of interaction in diametrically opposed directions. The simultaneous emission of the 511 keV photons is detected by pairs of opposing scintillation detectors connected by an electronic "coincidence" circuitry (Fig. 1). Only interactions occurring in the well defined "field of view" between each pair of detectors are recorded. This unique electronic collimation forms the basis of the depth-independent resolution. Like other photons, the two 511 keV X rays are attenuated as they travel through tissue, yet the degree of attenuation can be measured and, hence, corrected for appropriately. With use of these two principles, the distribution of positron-emitting indicators in the body can be determined by collecting data at multiple angles through a 180° arc. At present, this is best accomplished by tomographs using hexaganol, octagonal or circular arrays of detectors[1–3] (Fig. 2). From the recorded data cross-sectional or tomographic images are formed that display the distribution of radioactive-labeled tracers in a quantitative manner, that is, in terms of millicuries per picture element or gram of tissue. Therefore, these images resemble autoradiographs that are obtained in vivo or provide an in vivo capability that is analogous to in vitro counting of tissue samples (Fig. 3).

Availability of radioactive-labeled tracers: Radioactive indicators specific for various metabolic pathways are the second reason for the potential of positron emission computed tomography.[1–3] Table I lists several positron-emitting radionuclides that are used. For example, the isotopes of oxygen (O-15), carbon (C-11) and nitrogen (N-13) can be labeled to physiologic compounds without altering their biologic properties. Fluorine-18 also can be used to label chemical analogs of substrates by hydrogen or hydroxyl ion replacement. Table II list several of these radiopharmaceuticals labeled with positron-emitting radionuclides that are of potential value for the study of cardiac performance, myocardial blood flow and the metabolism of glucose, fatty acids and amino acids. The list includes only those compounds that have been evaluated at least to some extent.

The short physical half-life of these isotopes (1.2 to 110 minutes) limits a more widespread use of positron emission computed tomography because it requires an accelerator for the on-site production of these isotopes. Major efforts are therefore being devoted to the development of compact and dedicated cyclotrons that could be relatively inexpensive and reliable and operated like generator systems by technicians for fully or semiautomated production of labeled compounds.

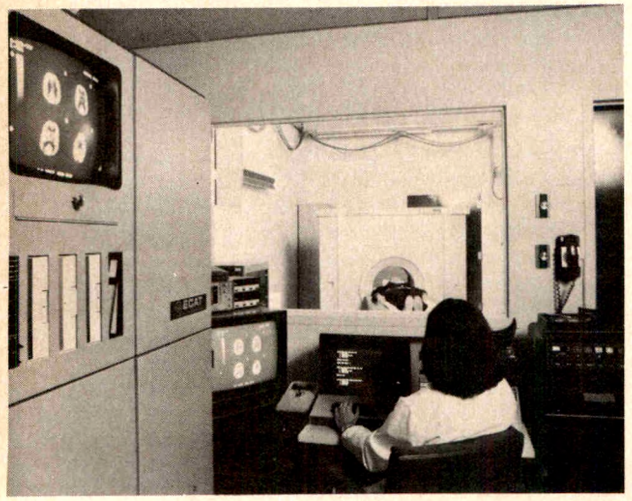


FIGURE 2. Whole body positron emission tomograph installed at the Nuclear Medicine Clinic, University of California, Los Angeles.



FIGURE 3. Typical cross-sectional images of the left ventricular myocardium obtained after intravenous administration of N-13 ammonia. The cross sections are spaced 1 cm apart. Levels 1 to 3 show the high anterior wall, level 4 the mid left ventricle and levels 5 and 6 the lower and diaphragmatic portions of the left ventricle. The images reflect quantitatively the distribution of N-13 activity throughout the myocardium. ANT = anterior; LAT = lateral; POST = posterior wall of the left ventricle; SEPTUM = interventricular septum.

TABLE I

Positron-Emitting Isotopes for Positron Emission Computed Tomography

Isotope	Physical Half-Life	Generator System	Generator Half-Life
Cyclotron-Produced			
Oxygen-15	2.03 min	...	...
Nitrogen-13	9.98 min	...	...
Carbon-11	20.4 min	...	...
Fluorine-18	110.0 min	...	...
Potassium-38	7.71 min	...	...
Rubidium-81	4.7 h	...	...
Generator-Produced			
Rubidium-82	75 s	Strontium-82 → Rb-82	25.0 days
Gallium-68	68.3 min	Ge-68 → Ga-68	287.0 days
Copper-62	9.7 min	Zn-62 → Cu-62	9.2 h

TABLE II

Positron-Emitting Radiopharmaceutical Agents Suitable for Cardiac Evaluation

Blood Pool Labeling Agents
Carbon-11 carbon monoxide Oxygen-15 carbon monoxide Gallium-68 red blood cells
Indicators of Blood Flow
Gallium-68 microspheres Copper-62 microspheres Potassium-38, rubidium-81, rubidium-82 N-13 ammonia
Indicators of Metabolism
Carbon-11 free fatty acids (palmitate) Fluorine-18 2-deoxyglucose Carbon-11 2-deoxyglucose Nitrogen-13 amino acids (glutamic acid; glutamine)[4]

However, there are significant advantages to the short physical half-life of these isotopes, namely, a small dose of radiation to the patient and the potential to perform repeat studies at short time intervals.

The need for on-site accelerators can be overcome to some degree by generator systems.[5–8] With these systems several isotopes suitable for positron emission computed tomography can be obtained in a manner that is similar to the elution of the widely used technetium-99m from the molybdenum-99 → technetium-99m generator (Table I). However, thus far the number of isotopes available through generator systems is limited. Moreover, incorporation of these isotopes into physiologic compounds without altering their biologic behavior has not been satisfactorily accomplished.

Conditions required for physiologic applications: Keeping in mind the two key elements of positron emission computed tomography (the autoradiographic nature of the images and the availability of physiologic tracers), how can one use this new imaging modality to measure regional myocardial perfusion and metabolism? Several conditions must be met before positron emission computed tomography can be used as a true and heretofore unknown "physiologic tomography" [9,10]: rigid characterization of the analytic capabilities of the imaging device for quantification of labeled tracer concentrations in tissue; delineation of the manner in which these tracers mimic a physiologic process; and, finally, physiologic modeling or mathematic formulation of tracer kinetic models so that physiologic variables can be derived from the imaging data.

Research efforts in our laboratory have stressed the study of these conditions in order to develop truly physiologic tomography. In the subsequent discussion we will evaluate each condition required for physiologic tomography and explain how it can be applied to the study of the three main aspects of myocardial performance: blood flow, mechanical function and metabolism.

Measurement of Regional Myocardial Blood Flow

Measuring myocardial indicator concentrations: Earlier we emphasized the autoradiographic nature of the cross-sectional images. In other words, these images reflect the distribution of tracer tissue concentrations in a quantitative manner and, hence, could be used to measure in vivo indicator tissue concentrations in terms of milligrams per gram of tissue. However, this capability is somewhat limited by the partial volume effect. Because of this limitation, positron emission computed tomography underestimates indicator tissue concentrations in anatomic structures that are small in comparison with the image resolution. As Hoffman et al.[11] demonstrated in phantom studies, if two objects with equal indicator concentrations but of considerably different volumes were imaged quantitatively, the concentration measured for the smaller object would be artificially small if its size were approximately two times less than the image resolution. Applied to the heart, positron emission computed tomography would underestimate indicator tissue concentrations in the 0.8 to 1.2 cm thick left ventricular myocardium by nearly 50 percent. Nevertheless, from the relation between concentration recovery and object size, the loss in concentration recovery can adequately be corrected for if the object size is known. Wisenberg et al.,[12] in our laboratory, recently demonstrated that this correction is indeed possible for the heart. During animal experiments, regional myocardial indicator tissue concentrations were measured in vivo with a high degree of accuracy after the concentrations derived from the positron emission computed tomographic images were corrected for wall thickness determined on postmortem examination or on echocardiography. This demonstration further confirmed the capability of positron emission computed tomography for the in vivo quantification of regional myocardial blood flow. With injection of gallium-68–labeled albumin microspheres into the left atrium and use of the arterial reference technique,[13] regional myocardial blood flow was accurately measured in vivo from electrocardiographic gated cross-sectional images of the left ventricle over a flow range from near 0 to 500 ml/min per 100 g. The standard error of the estimate over this large flow range was only

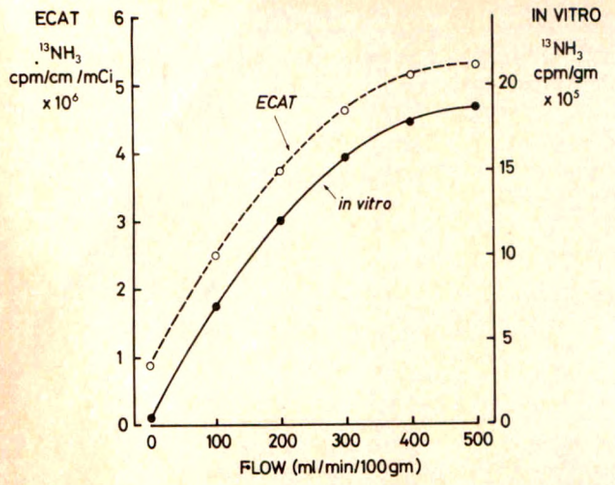


FIGURE 4. Relation between myocardial N-13 ammonia tissue concentrations and myocardial blood flow measured in vitro with the microsphere technique and in vivo with positron emission computed tomography (*ECAT*). The **solid line** represents the curve fit for N-13 ammonia concentrations measured in vitro, the **broken line** the curve fit for N-13 ammonia concentrations measured in vivo with positron emission computed tomography. Note the near linear relation over the flow range from 0 to 300 ml/min per 100 g. Further, both curves are virtually identical except for the upward shift of the in vivo curve which is due to instrument related background scatter and random coincidence, (Reprinted by permission from Schelbert et al.[21]).

12 ml/min per 100 g and the slope of the regression line between the in vivo and in vitro measurements was near unity (0.99).

Diffusible positron-emitting indicators of flow: Whereas particulate indicators such as radioactive microspheres are most accurate for blood flow measurements, their use in human beings is limited. They require administration into the left atrium or at least into the left ventricle. Further, because these indicators get trapped in capillaries they are of potential risk to organ perfusion, for example, perfusion to the brain. Therefore, a diffusible indicator is needed that can be administered intravenously and can readily cross the pulmonary circulation and become trapped in myocardium in proportion to blood flow. Several positron-emitting indicators have recently become available that may meet these requirements. Among these are potassium-38,[14] which is likely to exhibit the same characteristics as potassium-43, which has been used in the past as a flow indicator with gamma camera imaging. Budinger et al.[15] recently reported on the generator-produced short-lived rubidium-82 as an indicator for blood flow. This agent, considered a potassium analog, is likely to possess properties similar to those of potassium-43 and rubidium-81 (the latter is also a positron emitter and can be used with positron emission computed tomography). Initial results with this agent are promising, yet its ultrashort physical half life of 75 seconds may require specifically designed administrative schedules.

Nitrogen-13 ammonia for measuring regional myocardial blood flow: We extensively evaluated another agent, nitrogen-13 ammonia, which was initially used as a myocardial imaging agent.[16–18] Administered intravenously, N-13 ammonia is distributed in proportion to blood flow and rapidly and almost completely clears from the blood into the myocardium where it is trapped sufficiently long to permit quantitative imaging.[19–21] With these properties, N-13 ammonia resembles to some degree a particulate indicator. At control flow (80 ml/min per 100 g) the extraction of N-13 ammonia during a single capillary transit approaches 90 percent[17] but decreases as flow increases.[21] Within the range of physiologically encountered flows (for example, from near 0 to 300 ml/min per 100 g) myocardial tissue concentrations are almost linearly related to myocardial blood flow (Fig. 4). Except for extreme changes in arterial plasma pH levels, trapping of N-13 ammonia in the myocardium remains unaffected by alterations in the metabolic and functional state of the heart (unpublished data). There is evidence that because N-13 ammonia rapidly clears from the blood and is quickly trapped and fixed in the myocardium (blood levels of N-13 ammonia are less than 2 percent of peak activity within 5 minutes of injection) noninvasive quantification of regional myocardial blood flow with this agent may be possible.[22]

Detection of coronary stenosis: The suitability of this new agent for the assessment of regional myocardial blood flow with positron emission computed tomography has been demonstrated in experimental animals[21,23] and, more recently, in human beings.[24] We[24] have further shown the potential value of N-13 ammonia and positron emission computed tomography in detecting mild coronary arterial stenoses. At rest, even moderately severe coronary stenoses may not alter coronary blood flow, yet they limit the coronary flow reserve. Conversely, coronary flow reserve may be reduced by very mild stenoses, a phenomenon that can be demonstrated during maximal coronary vasodilatation.[25] Using this technique in chronically instrumented animals we were able to detect narrowing of coronary stenoses with less than 50 percent in diameter with N-13 ammonia and positron emission computed tomography during pharmacologically induced vasodilatation.[23] These findings are currently being tested in human subjects (Fig. 5). Our results in 10 normal volunteers and 29 patients with coronary artery disease appear to confirm these initial data in animals and indicate that coronary stenoses as low as 40 percent in diameter narrowing can indeed be identified.[24]

Assessment of Regional Mechanical Function

Regional myocardial function is conventionally determined from the extent and time course of regional systolic wall motion and thickening. These variables are conventionally derived from contrast cineventriculography,[26] echocardiography[27] or electrocardiographic gated blood pool imaging.[28] As in the latter method, the positron computed tomograph can be synchronized with the patient's electrocardiogram and gated cross-sectional images obtained either at end-diastole and end-

systole or as a sequence of images throughout the entire cardiac cycle.[29]

Regional wall motion: From the gated cross-sectional images of the left ventricular myocardium or the cardiac blood pools—visualized after inhalation of small amounts of C-11 carbon monoxide that binds to hemoglobin and is an excellent blood pool imaging agent—quantification of left ventricular wall motion and global left ventricular function will be possible in the near future. As Nichols et al.[30] recently demonstrated in patients with coronary artery disease, it is also possible to evaluate indirectly the functional reserve of the left ventricle by positron emission tomography by monitoring the changes in cardiopulmonary blood volume during exercise.

Regional wall thickening: Furthermore, regional wall thickening may be a highly sensitive index of regional myocardial function[31] that can be determined from gated cross-sectional images of the left ventricular myocardium. We mentioned earlier the difficulties in concentration recovery related to object size. Although this dependency complicates the quantification of tissue concentrations it can be utilized to measure systolic wall thickening. As shown recently in our laboratory,[12] the counts recovered from a given myocardial segment and expressed in counts/min per gram of tissue increase from end-diastole to end-systole. The increase is proportional to the degree of wall thickening as measured with echocardiography. If applied to human subjects, measurements of regional myocardial blood flow could be combined with determinations of regional mechanical function and both measurements correlated. It would also seem feasible to expand this concept to comparison of regional myocardial function with metabolism provided the myocardium is visualized with a metabolic tracer.

Assessment of Regional Myocardial Metabolism

Numerous techniques have been developed and successfully used for evaluating regional myocardial blood flow and function either invasively or noninvasively. However, the in vivo study of regional myocardial metabolism has thus far been unsatisfactory. It is in this area where positron emission computed tomography shows the greatest promise and where its unique potential lies.

Available metabolic isotope tracers: This potential is attributable to the quantitative capabilities of the imaging device and to the availability of radiopharmaceutical agents that are highly specific indicators of metabolic pathways. We discussed earlier the isotopes that can be labeled to naturally occurring compounds without altering their biologic behavior. Although it would seem logical to label metabolic substrates, the difficulties encountered with this approach can be illustrated by the example of labeled glucose. Glucose as a primary energy substrate can be tagged with carbon-11 (C-11) but its chemical state in myocardium at any time after intravenous administration remains unknown to positron emission computed tomography. The measured C-11 tissue concentrations represent a complex

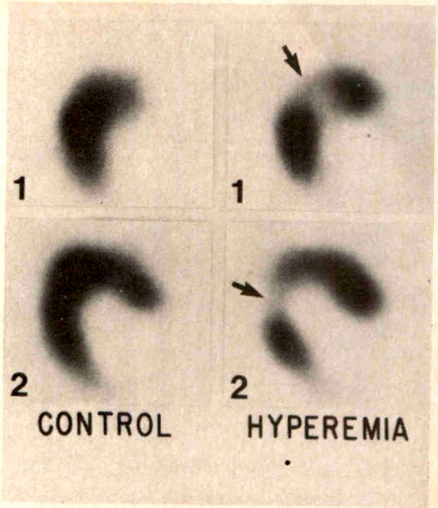


FIGURE 5. Cross-sectional myocardial perfusion images obtained with N-13 ammonia during a control period and during dipyridamole-induced coronary vasodilatation. Only the high to mid anterior wall is shown (1 and 2). In the control period the images are normal; however, during hyperemia, a defect is evident in the anterior wall (**arrows**) corresponding to a stenosis of the left anterior descending coronary artery.

distribution of compounds that change with time. Further, its rapid turnover rate in the myocardium poses some limitations on the acquisition of high contrast cross-sectional images.

It thus would seem preferable to use radioactive tracers that are not only specific for a given metabolic pathway but are also retained in the myocardium sufficiently long to permit adequate external imaging and to trace a metabolic process in a known and well defined manner that is amenable to physiologic modeling.[9,10] Past research has therefore focused on two radiopharmaceutical agents—C-11 palmitate and F-18 deoxyglucose (FDG)—both of which appear largely to fulfil the requirements of physiologic tomography. Moreover, they seem particularly intriguing for the study of cardiac metabolism because the role of glucose and free fatty acids as the primary energy substrates of the heart has been well establisbed.

C-11 palmitate for assessing fatty acid metabolism: Carbon-11 palmitate has been described as a myocardial imaging agent suitable for positron emission computed tomography[32,33] and more recently has been used for sizing myocardial infarcts in human beings.[34] Beyond its use for myocardial imaging, this agent may eventually prove useful for assessing fatty acid metabolism of the heart. Because the C-11 label does not alter the biologic behavior of palmitate, the total uptake in myocardium or its turnover rates should, in theory, provide a measure of the rate of fatty acid metabolism. This hypothesis appears confirmed by Goldstein,[35] Klein[36] and their co-workers, who observed in the isolated perfused rat heart an inverse relation between myocardial half-times of C-11 palmitate and cardiac work. Further, the myocardial tissue half-time was

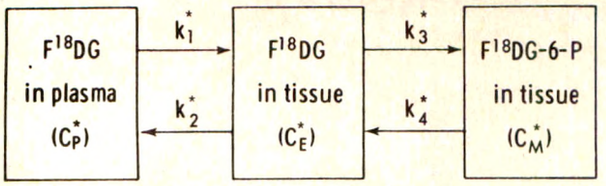


FIGURE 6. Three compartment tracer kinetic model for the kinetics of F-18 2-fluoro-2-deoxyglucose ($F^{18}DG$) (see text).

markedly prolonged under ischemic conditions.[33] Although these results are encouraging, their application to the in vivo situation with recirculation of indicator and flow dependency of indicator delivery and washout is highly complex and awaits further clarification.

Moreover, the intracellular kinetics of free fatty acids and hence of C-11 palmitate are very complex and exemplify the difficulties in measuring regional myocardial metabolic rates in vivo. On entering the myocardial cell, free fatty acids are either channeled directly into beta oxidative pathways, incorporated into phospholipids or stored in the form of triglycerides. It appears that a large fraction of fatty acids entering the cell is initially stored in the form of triglycerides. External measurements of myocardial C-11 palmitate uptake would therefore not strictly reflect the rate of fatty acid utilization. Conversely, myocardial half-times of C-11 activity would indicate primarily the rate at which triclycerides are hydrolyzed. The rate of fatty acid utilization thus could be deduced only by inference, provided that all of the hydrolyzed fatty acids enter beta oxidation without any loss into the blood. Accurate measurements of fatty acid utilization are therefore possible only if (1) the various segments of the fatty acid metabolism can be identified and delineated; or (2) when measuring total myocardial uptake, the ratio of fatty acids entering beta oxidation to fatty acids converted to triglycerides is constant; or (3) when measuring myocardial half-times, the rate of fatty acid oxidation is in constant proportion to the rate of triglyceride hydrolysis. It is conceivable that the complex kinetics of natural compounds cannot be defined sufficiently to permit accurate measurements of myocardial metabolic rates; substrate analogs must be developed that trace only one segment of a metabolic pathway, yet can be better delineated, their kinetics expressed in the form of a physiologic model and formulated in mathematic terms.

F-18 deoxyglucose for measuring regional glucose utilization rates: Radioactive-labeled 2-deoxyglucose has become available as such a substrate analog for the measurement of regional glucose utilization rates. Sokoloff et al.[37] labeled this agent with C-14 and originated a physiologic model for measurements of local cerebral glucose utilization in vitro. To adopt this technique for in vivo positron emission computed tomographic measurements, the 2-hydroxy group was substituted by an F-18 atom to yield F-18 2-fluoro-2-deoxyglucose (FDG).[38,39] Huang et al.[40] modified the original physiologic model, and measurements of regional cerebral glucose metabolism with this technique were subsequently validated by Phelps et al.[41] Once administered intravenously, both exchange of FDG across capillary and cell membranes as well as initial metabolization are similar and proportional to those of glucose. Like glucose, FDG is phosphorylated by hexokinase to FDG-6-PO_4. It then becomes metabolically trapped and is not a substrate for glycolysis, glycogen formation or the pentose shunt. Metabolically unbound FDG subsequently clears from the myocardium and positron emission computed tomographic images obtained at equilibrium reflect the regional utilization rates of exogenous glucose.

The kinetics of F-18 2-fluoro-2-deoxyglucose can be expressed by a three compartment tracer kinetic model with exchange among compartments that follows first order kinetics.[40,41] This is shown schematically in Figure 6, where k_1^* and k_2^* are the rate constants for forward and reverse transport across the capillary and cell membranes and k_3^* and k_4^* the rate constants for phosphorylation and dephosphorylation between FDG and FDG-6-PO_4. Our initial findings suggest that the rate constants of FDG in myocardium are similar in magnitude to those in the brain.[42] Once established they will be incorporated together with the physiologic model into the tomograph's systems program[42–44] so that regional myocardial utilization rates can be determined routinely by trained technicians in nuclear medicine. For this measurement, FDG is administered intravenously and venous blood sampled serially. After 40 to 50 minutes, when near steady state conditions are reached, cross-sectional imaging is performed, plasma glucose and FDG levels obtained and entered into the tomograph's systems computer; regional myocardial glucose utilization rates are then calculated automatically from selected regions of interest.[43] The accuracy of these measurements for the brain has been documented, but that for the heart awaits validation. Nevertheless, our initial experience has been encouraging. Regional glucose utilization rates calculated with this noninvasive approach ranged from 5 to 20 mg of glucose/min per 100 g and thus are in close agreement with data derived invasively in our laboratory in experimental animals using the Fick method (unpublished data).

Clinical Applications

Thus far, we have discussed the technical aspects of positron emission computed tomography and its potential as a new means for the noninvasive study of regional myocardial blood flow, mechanical function and regional metabolism. Considering the complexities, effort and cost involved, the question as to whether this new study means will be clinically feasible and cost effective seems appropriate. Our initial clinical experience with this new tool in patients with cerebral disease is very encouraging and suggests that metabolic abnormalities of the brain detected with physiologic tomography provide an improved understanding of cerebral function.[45,46] In these studies, the metabolic abnor-

malities correlated better with the clinical symptoms than with the structural or anatomic alterations revealed by computed tomographic (CT) scanning.[45] Whether this also applies to the heart is at present uncertain and will likely be answered in the near future.

Detection of coronary arterial stenosis: Physiologic tomography offers a unique and heretofore unknown potential for the study of regional myocardial physiology and pathophysiology. We mentioned earlier our initial observations on the detection of coronary arterial stenoses in the experimental animal[23] and in the human subject.[24] In these studies, detection of single vessel disease in human subjects was highly accurate and appeared superior to that obtained with conventional imaging. Stenoses with only 40 percent diameter narrowing on coronary arteriography were correctly identified. In about 50 percent of patients with triple vessel disease, the technique identified only two of the three diseased coronary arteries. The vessels not detected were usually those with the least severe stenosis. Image analysis in these studies was only qualitative and the segment supplied by the least severely stenosed coronary artery was used as reference. However, if the response to pharmacologic coronary vasodilatation is reproducible and consistent from patient to patient then the absolute increase in segmental myocardial blood flow should be a superior index for the presence and severity of a coronary stenosis. Quantification of region myocardial blood flow with positron emission computed tomography appears possible by measuring the arterial input function and the local myocardial N-13 ammonia concentrations.

Study of myocardial metabolic alterations in acute ischemia: As another example, this new study technique may, for the first time, permit characterization of the local metabolic alterations associated with acute myocardial ischemia. In preliminary animal experiments we[47] applied a graded stenosis to the left anterior descending coronary artery and induced ischemia by pacing at high rates. Myocardial perfusion assessed with N-13 ammonia and positron emission computed tomography was reduced in the ischemic segment. F-18-2-fluoro-2-deoxyglucose concentrations as an index of regional glucose utilization were decreased in the ischemic segment, yet were disproportionately less than blood flow (Fig. 7). Quantitative correlation between perfusion and the glucose uptake in the cross-sectional images demonstrated glucose uptake in excess of flow in the ischemic segments. If blood flow reflects the oxygen availability (that is, if the net extraction of oxygen does not considerably increase at reduced flows), then these observations suggest that energy in the ischemic segment is primarily derived from glucose either by residual oxidative capacity or by anaerobic glycolysis, or by both, as suggested by Opie et al.[48] Of interest in this context is the recent demonstration[49] of accumulation of F-18 in infarcted myocardium. Comparison of FDG and F-18 images in acute myocardial ischemia thus may allow evaluation of ischemic segments with respect to cell viability and irreversible cell injury. Should this approach be applicable to human subjects it may become possible to identify ischemic myocardium, characterize its metabolic state and the degree of cell viability. It may also be of value in monitoring the effects of therapeutic interventions designed to salvage injured myocardium. Because the severity of ischemia depends not only on blood flow but also on the mechanical demand as well as the duration of the insult (all of which are at present difficult if not impossible to assess) physiologic tomography may provide the most accurate means for estimating the severity of ischemia.

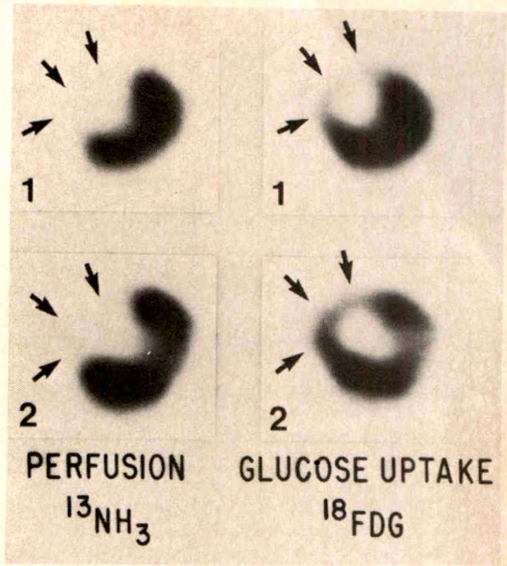


FIGURE 7. Cross-sectional images obtained in a dog during pacing-induced ischemia of the anterior wall. Note the extensive perfusion defect in the perfusion images (**arrows**); a defect is also evident in the glucose uptake images, but is considerably less pronounced and suggests glucose utilization in excess of blood flow (see text).

Clinical Implications

The examples described were intended to illustrate the potential of physiologic tomography and to evaluate the type of information that can be obtained with this new means of studying cardiac performance. It is conceivable that such data prove to be clinically useful and relevant. Nevertheless, the utility and ultimate clinical role of this new imaging technique are difficult to assess and need to be defined in the future. However, we believe that the current improvement in instrumentation, the development of compact, reliable and generator-like cyclotrons or development of radiopharmaceutical agents labeled with positron emitters (available through generator systems) will greatly facilitate the use of physiologic tomography and make it accessible to a larger number of users. Physiologic tomography already represents an important new tool for investigative studies to improve our understanding of cardiac physiology and disease. The quantitative aspects as well as simultaneous evaluation of more than one aspect of myocardial performance—for example, simultaneous

study of mechanical function, blood flow and metabolism and their interdependency—will provide a new and better understanding of myocardial physiology. Because many of the cardiovascular disorders originate at the cell or metabolic level it is hoped that this technique may serve as a means for the early detection of cardiac disease, perhaps at a stage when it is still amenable to therapy.

Acknowledgment

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Nuclear Magnetic Resonance Imaging: Potential Cardiac Applications

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During the past several years, the production of high resolution images of organs in intact animals and human beings using nuclear magnetic resonance (nmr) has generated much interest and raised the possibility that the technique could be usefully applied to clinical problems. Because the images are derived from biochemical as well as structural information, valuable data relating to the metabolic status of the tissues and organs may be obtained. Furthermore, nuclear magnetic resonance imaging involves no potentially hazardous ionizing radiation. The technology of the technique is complex and much work remains to be done defining the biochemical and physiologic basis of such images, but the potential rewards of defining the metabolic state of organs such as heart and brain in the intact animal and human justify continued research.

Since 1977, high resolution images of organs in intact animals formed by the technique of nuclear magnetic resonance (nmr) have been produced by several laboratories. This method of imaging is attractive because it avoids the use of ionizing radiation and tracer administration and potentially could provide metabolic as well as anatomic information.

Nuclear magnetic resonance is one of the newest methods of probing the electromagnetic spectrum of atoms and molecules. Although first described in the 1940's, it was only recently that the technique was applied to studies of biologic samples. The approach was slow to find application in biologic systems because it lacked sensitivity for detection of relevant nuclides. In addition, the complexity of organized living systems presented a difficult challenge for the technique. Before 1974 nuclear magnetic resonance studies of biologic systems were limited to examination of purified biologic materials such as protein solutions, lipid bilayers and ions. In 1974 nuclear magnetic resonance studies relating to metabolic function of intact red blood cells[1,2] and intact living muscle[3,4] were published. This was the beginning of the realization that detailed useful data could be extracted from nuclear magnetic resonance spectra of complete biologic systems.

The feasibility of using nuclear magnetic resonance to produce images depicting spatial distribution of nuclei was first demonstrated in the early 1970's by Lauterbur.[5,6] The intervening years have seen a dramatic expansion in the field of nuclear magnetic resonance imaging. Early successes in the field[7–10] have sparked an interest in many laboratories in developing nuclear magnetic resonance imaging into a clinically useful diagnostic tool.

Nuclear Magnetic Resonance (nmr) Spectroscopy

Comprehension of the approach to nuclear magnetic resonance imaging requires at least a preliminary understanding of nuclear magnetic resonance spectroscopy. Many of the elements of the periodic table have isotopes that, by virtue of their quantum spin numbers, have magnetic moments. Although the analogy is an oversimplification, these

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atomic nuclei behave as though they were tiny bar magnets (Fig. 1). The isotopes most easily observed with nuclear magnetic resonance are: hydrogen (protons), fluorine-19, phosphorus-31 and carbon-13.

In the presence of an externally applied magnetic field, the relevant atomic nuclei align themselves either parallel or anti-parallel to the field (Fig. 2), and they precess, or rotate, much as a child's spinning gyroscope precesses in the earth's gravitational field when tipped from its vertical position. If these nuclei are then disturbed, or tilted from their equilibrium alignments by a pulse of radiofrequency radiation (Fig. 3), the precessing nuclei return to their ground state of equilibrium by emitting low energy radiofrequency signals that are detected by a tuned antenna coil and amplified (Fig. 4). Frequency analysis of the emitted signal is accomplished by Fourier transformation and the nuclear magnetic resonance spectrum is displayed as a plot of intensity of signal versus frequency. The emitted signal is generally very low except at the resonant frequency of the nucleus where a peak is observed. The resonant frequency is, in fact, the frequency of precession of the nucleus in a given magnetic field.

Because the resonant frequency of a nucleus is a function of both its magnetic moment and the effective magnetic field at the nucleus, chemical interactions affecting the electron cloud surrounding the nucleus change the effective field and alter or shift the resonant frequency, allowing separation and identification of different chemical species. An example of a phosphorus nuclear magnetic resonance spectrum illustrates this concept (Fig. 5). The ability to observe separately and quantitate different chemical species is the basis of nuclear magnetic resonance spectroscopy.

Other useful information obtainable by nuclear magnetic resonance are relaxation times. As the precessing nuclei excited from a radiofrequency pulse give up energy in the form of emitted radiation, they relax to their equilibrium positions exponentially with a time constant T_1. T_1 is called the spin-lattice relaxation time. The relaxation variable of protons, for example, provides useful information about water structure and allows detection of subtle changes in tissue.

Because nuclear magnetic resonance-emitted signals are weak and thermal motion obscures the signal, thus resulting in a poor signal to noise ratio, the samples are generally studied multiple times with repeated pulses of radiofrequency energy and the emitted signal is time-averaged. Because thermal noise is random, the time average of thermal noise is zero; thus the more pulses, the higher the signal to noise ratio.

Nuclear Magnetic Resonance Imaging

In the early 1970's Lauterbur recognized that nuclea magnetic resonance could be used to construct images The resonant frequency of a sensitive nuclide is proportional to the magnetic field at the nucleus: $\omega = \gamma H$ where ω is the resonant frequency, γ is a constant fo a given nuclide, called the gyromagnetic ratio, and H i the magnetic field. For nuclear magnetic resonanc spectroscopy, the magnetic field is uniform. If th magnetic field is made inhomogeneous by superimposing magnetic field gradients over the main homogeneous field, it is possible to attach spatial informatio to the emitted signal and thereby reconstruct image (Fig. 6).

Several methods have been devised for inscribin spatial data on the nuclear magnetic signal. One suc

■ *Random nuclear moments.*

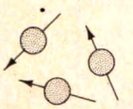


FIGURE 1. Sensitive nuclei have random magnetic moments in th absence of a magnetic field.

■ *Uniform magnetic field aligns magnetic moments*

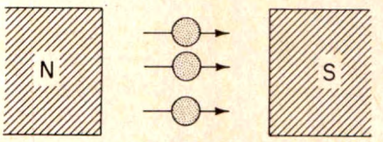


FIGURE 2. In the presence of an externally applied uniform magnetic field, the magnetic moments align themselves parallel to the field N = north; S = south.

■ *Applied* RF *burst perturbs magnetic moments.*

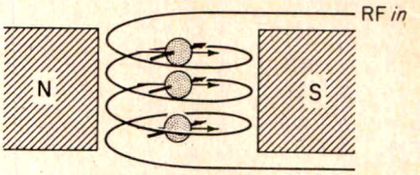


FIGURE 3. An appropriately timed radiofrequency (RE in) pulse pertirbs the equilibrium distribution of the magnetic moments.

■ *Realignment emits characteristic frequency sensed by* RF *coil*

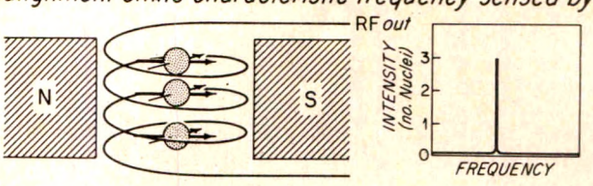


FIGURE 4. As the perturbed nuclei relax to equilibrium, the emitted radiofrequency signal (RF out) is sensed by a suitably tuned radiofrequency (RF) coil (antenna). Fourier transformation of the signal produces the nuclear magnetic resonance spectrum. The resonant frequency appears as a sharp peak on the intensity scale. no. = number.

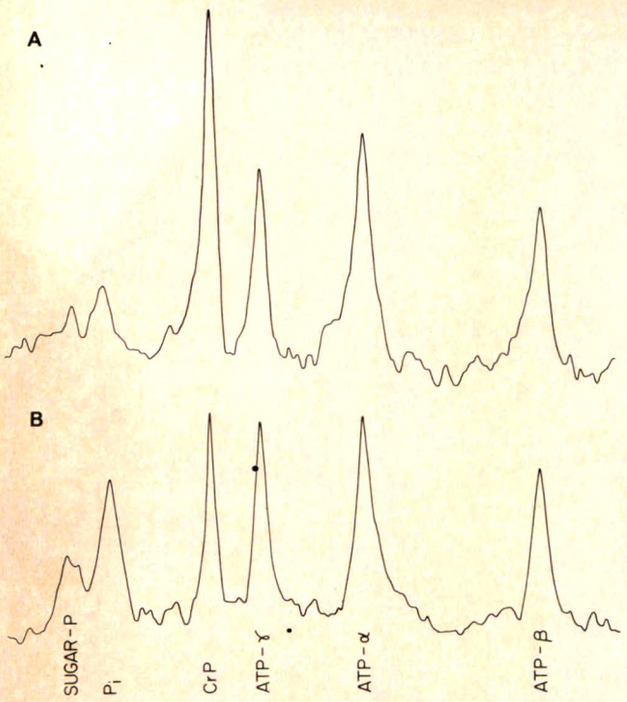


FIGURE 5. Representative phosphorus-31 nuclear magnetic resonance spectra from isolated perfused rat hearts. **A,** spectrum from a Langendorf heart. **B,** spectrum from a working perfused heart. Note that the working heart has less creatine phosphate and more inorganic phosphate (Pi). γ, α and β represent the three phosphate groups of adenosine triphosphate (ATP).

approach, the "sensitive point" technique, pioneered by Hinshaw et al.[11], has thus far produced the highest quality images of biologic tissue. In this approach, rapidly alternating orthogonal (perpendicular) magnetic field gradients are superimposed on the static field. By adjusting the gradients appropriately, a single point, or line, in the sample is isolated in the imaging space where the alternating gradients are null. The alternating field gradients are analogous to a child's seesaw. A time exposure photograph of the seesaw when it is moving up and down will be blurred except at the fulcrum. The fulcrum is analogous to the "sensitive point." It is from this point or line that the nuclear magnetic resonance signal is gathered and stored in the computer or displayed directly. The signals from all other locations are eliminated. The sensitive locus can then be moved electronically through the sample by adjusting the field gradients and the completed image displayed as a tomogram or a projection (Fig. 7).

The image data obtained using this technique are intrinsically three dimensional and, with use of computer techniques, three dimensional image reconstruction is possible as well as tomographic display. To date, tomograms with less than 0.5 mm resolution have been made of various vegetables and fruits (Fig. 8), a rabbit's head and a human wrist.[11,12] An advantage of this technique is that there are no moving parts in the instrument. The sensitive locus is moved entirely by electronically adjusting the magnetic field gradients. The time required to produce a nuclear magnetic resonance image depends on many factors: the size of the sample, the method of constructing the image, the resolution desired, the signal to noise ratio and, therefore, the quality of image desired. With optimization of all these factors it should be possible to obtain reasonable quality nuclear magnetic resonance images of human-sized objects in a clinically acceptable time.

Biologic Imaging Applications of Nuclear Magnetic Resonance

Nuclear magnetic resonance imaging offers the opportunity to gather spatial biochemical information on intact and functional biologic systems. Because water is the major component of every biologic system and protons are the most sensitive of nuclei to nuclear magnetic resonance observation, the protons of water are the most conspicuous component of tissue with which to generate a nuclear magnetic resonance image. Water constitutes 80 percent of muscle and 90 percent of brain and blood. In tissue damaged by ischemia the water content can increase by as much as 20 to 30 percent. It has been found that the relaxation variable T_1 is a function of the type of tissue and, importantly, can be significantly different in normal and diseased tissues. Although it was initially suggested that changes in relaxation properties of tissue are simply and only a reflection of the water content, these variables have been shown to be affected by additional factors that may have importance to the structure of water in the cell. These factors include the protein content and state of association (that is, the structure of water), ionic strength and composition, cell pH and probably other factors yet to be defined. The characteristics of the nuclear magnetic resonance signal of water (both content and T_1) might therefore provide a sensitive means for defining structures and identifying diseased tissue by nuclear magnetic resonance imaging.

Some nuclear magnetic resonance measurements of water in heart have been made.[13,14] These reports, coupled with several basic studies of myocardial edema due to ischemia, suggest that there may be differences

■ *Magnetic field gradient makes frequency position dependent.*

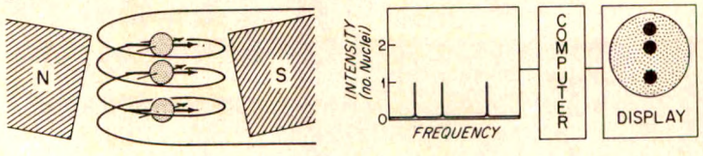


FIGURE 6. Because the resonant frequency of a nucleus is a function of the magnetic field at that nucleus, the imposition of a field gradient allows spatial separation of sensitive nuclei. Nuclei with the same magnetic moment have a greater resonant frequency in a stronger magnetic field than in a weaker one. Various methods of gradient production and image reconstruction have been used to produce nuclear magnetic resonance tomograms.

in the proton nuclear magnetic resonance signal that could be used to distinguish between ischemic and normal areas. In a series of experiments on dog hearts subjected to coronary arterial ligation by Lauterbur et al.,[14] nuclear magnetic resonance studies of serial biopsy specimens demonstrated that (1) water content increases in ischemic tissue, (2) T_1 values change in parallel with ischemic damage, and (3) administration of the paramagnetic ion manganese dramatically alters T_1 values in the compromised tissue. These results suggest that proton nuclear magnetic resonance of the heart might allow clinical differentiation between normal and ischemic tissue.

It is entirely conceivable that proton nuclear magnetic resonance imaging will be able to identify, depict and quantify ischemic myocardial injury, either in the acute phase or chronically. The detection of these areas based on biochemical information may allow measurement of infarct size, extent of the ischemic zone and therefore the amount of myocardium in jeopardy. The nuclear magnetic resonance technique could even be combined with maneuvers such as exercise to depict and quantify the changes associated with ischemia.

The use of phosphorus-31 nuclear magnetic resonance to study myocardial ischemia and infarction offers a method to evaluate endogenous compounds that are actively and directly linked to organ function. Large changes occur in the concentration, rates of utilization, and synthesis of adenosine triphosphate (ATP) and creatine phosphate (CrP) during ischemia. These changes follow loss of myocardial contractile function and precede ultrastructural derangements and cytoplasmic enzyme depletion. As recently discussed by Kubler and Katz,[15] changes in concentrations of ATP or CrP in specific cell compartments may regulate the energy-dependent processes of contraction and ion transport. It is possible that the extent of depletion of high energy phosphates is an important determinant of return of function, that is, viability.

Because ATP, CrP and inorganic phosphate can be distinguished with nuclear magnetic resonance spectroscopy, the characteristics of high-resolution phosphorus (P) 31 nuclear magnetic resonance spectra may permit definition of reversible and irreversible ischemic

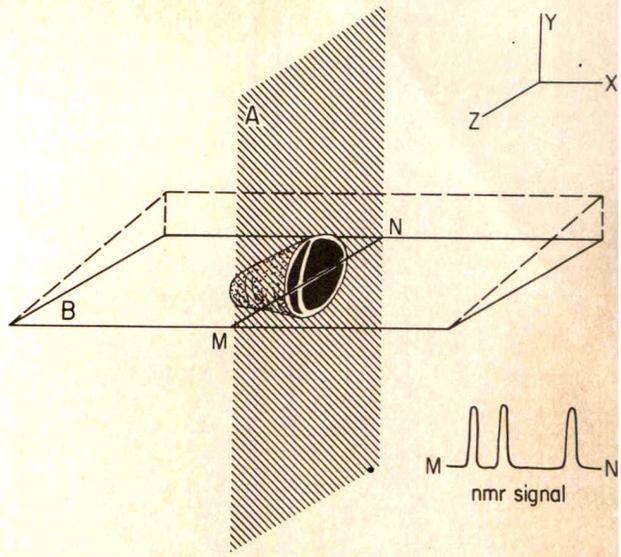


FIGURE 7. Time variant gradients along the X and Y axes define planes A and B, respectively, where the gradients are null. The intersection of A and B is a line along the Z axis, MN. If a static magnetic gradient is applied along the Z axis, the nuclear magnetic resonance (nmr) signal recorded is a projection along line MN (**lower right**). By adjusting the time variant gradients, line MN may be moved anywhere in the imaging volume. Computer image reconstruction of the object can then be performed.

damage to the myocardium. ATP, CrP and inorganic phosphate have been measured in intact beating rat hearts with use of nuclear magnetic resonance.[16] At the onset of ischemia, CrP concentration decreases rapidly; ATP concentrations decrease more slowly. Inorganic phosphate increases stoichiometrically. If ischemia is transient, the concentrations of high energy phosphates return toward normal. However, if cell death occurs, not only do the levels of ATP and CrP remain low, but also inorganic phosphate will eventually wash out, identifying infarction. In addition to monitoring the decrease in ATP and CrP during ischemia, Jacobus et al.,[17] used phosphorus-31 nuclear magnetic resonance positions to monitor changes in intracellular pH.

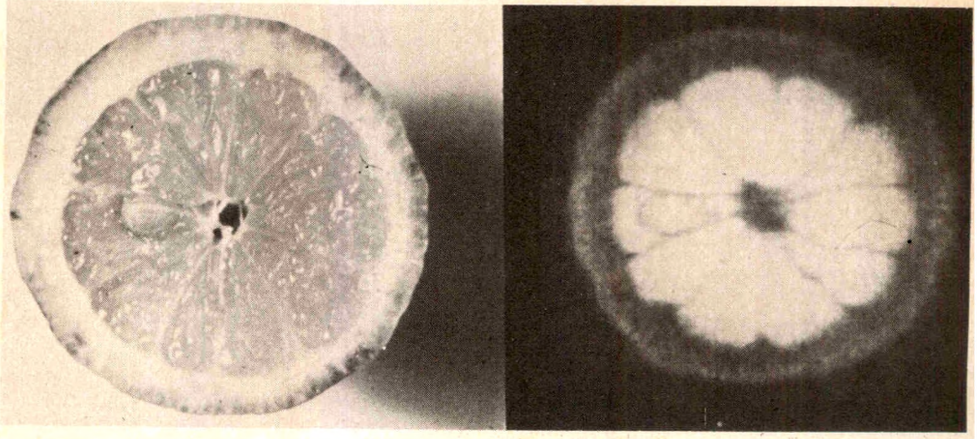


FIGURE 8. Right, nuclear magnetic resonance proton image of an uncut lemon. Note the fine detail of the septa and the seed. The resolution is substantially less than 1 mm. **Left,** photograph of the lemon at the level of the imaging plane. (Reproduced with permission of *Nature* and Waldo S. Hinshaw, PhD.)

The potential clinical use of nuclear magnetic resonance to obtain detailed biochemical information reflecting cell viability would be an extraordinary means for identifying, quantifying and understanding the ischemic process. The natural history of the ischemic process, the assessment of efficacy of medical and surgical intervention and improved understanding of the pathophysiology of ischemic disease are all potential rewards of this approach.

Unresolved Problems

As with any new technique, nuclear magnetic resonance imaging has many unresolved potential problems. The most important of these are safety of the technique, organ motion, radiofrequency penetration and sensitivity.

Safety: There is no known hazard associated with nuclear magnetic resonance imaging. People exposed to high level magnetic fields near particle accelerators for many hours have had no ill effects. The radiofrequency energy loss in the tissues has been calculated to be well below the recommended maximal long-term exposure of 10 milliwatts/cm^3. Patients with a cardiac pacemaker present special problems because most pacemakers operate in a fixed rate mode in a strong magnetic field and may compete with a spontaneous rhythm. Furthermore the electrode may conduct induced currents and initiate arrhythmias. Human beings have undergone imaging without incident. Human images made thus far include an image Mansfield[18] made of his own abdomen, Hinshaw's image[19] of a human wrist and images of the head made by investigators employed by EMI Corporation.[19] Nuclear magnetic resonance imaging does not involve ionizing radiation such as that associated with X-ray or radionuclide techniques.

Organ motion: Motion of an organ such as the heart during nuclear magnetic resonance imaging may present problems not applicable to static imaging. It may be possible, by electrocardiographic gating of the radiofrequency pulsing sequence, to collect nuclear magnetic resonance images in a fashion analagous to that used with the gated blood pool scan. This and other approaches remain to be investigated.

Radiofrequency penetration: The ability to image an organ with nuclear magnetic resonance relies on the ability to excite all the relevant nuclei in the sample. If the pulsing radiofrequency signal cannot penetrate the sample (organ or body), the technique fails and images will not be produced. Or, the images may be reconstructed with unacceptable distortion. Radio frequency penetration is inversely related to the frequency, and rough estimates of radio frequency penetration have been made based on saline models. Whether these estimates are accurate approximations in human tissue is not known at this time. It is unlikely that radio frequency penetration will be a serious problem for proton nuclear magnetic resonance imaging, although with other nuclides it may be a formidable challenge.

Sensitivity: Lastly, the sensitivity of the particular nuclide to detection by nuclear magnetic resonance and the concentration of the nuclide are the most important factors in producing useful images. Protons, which are highly abundant in biologic systems and are easily detectable with nuclear magnetic resonance, represent the best possible imaging agent. In contrast, phosphorus is present in relatively low concentration in cardiac tissue and is less than 10 percent as susceptible to detection by nuclear magnetic resonance as protons. Generating nuclear magnetic resonance images of phosphorous-31 distribution with acceptable signal to noise ratios with even coarse resolution will be a significant challenge. Even if high resolution images of phosphorus-31 distribution were technically impossible, valuable metabolic information might be obtained from the entire heart or large segments (for example, the anterior wall) by analyzing the phosphorus nuclear magnetic resonance spectrum from that large volume. One could envision using other methods such as radionuclide techniques to identify regions of myocardium and then using nuclear magnetic resonance data to assess viability in that region. Or, the metabolic status of the region could be assessed during or after various interventions, either pharmacologic, surgical or exercise-induced. Because the limitations of the approach are still unknown, the potential applications in cardiology as well as all medicine remain vast.

Clinical Implications

Nuclear magnetic resonance imaging is in its infancy and its potential applications are both innovative and exciting. The ability to extract biochemical and metabolic information from images noninvasively would be a powerful aid in diagnosing disease. The differentiation of ischemic from infarcted and normal tissues using biochemical rather than structural or flow-dependent imaging methods is a real potential for nuclear magnetic resonance imaging and not possible using other techniques. As the field develops we look forward to improved technology, better image quality and solutions to the problems outlined.

Acknowledgment

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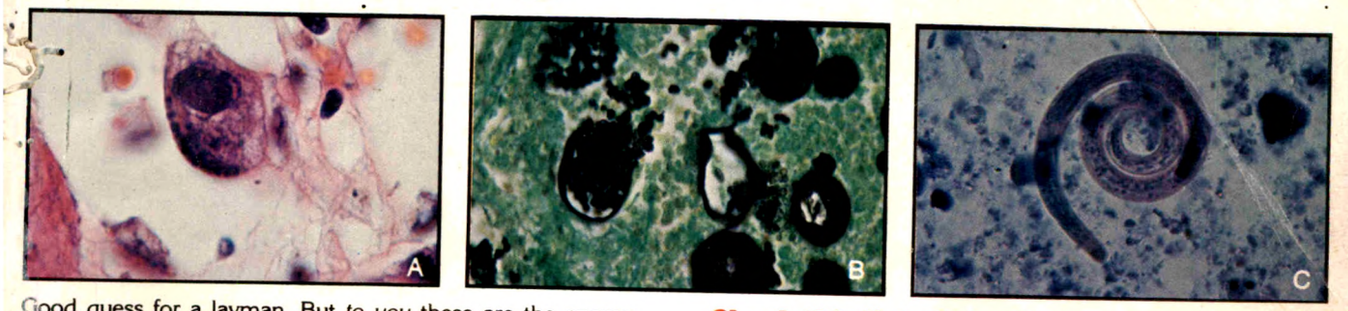
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Paintings by Jackson Pollock?



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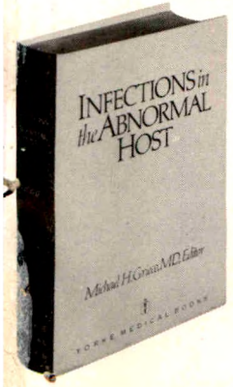
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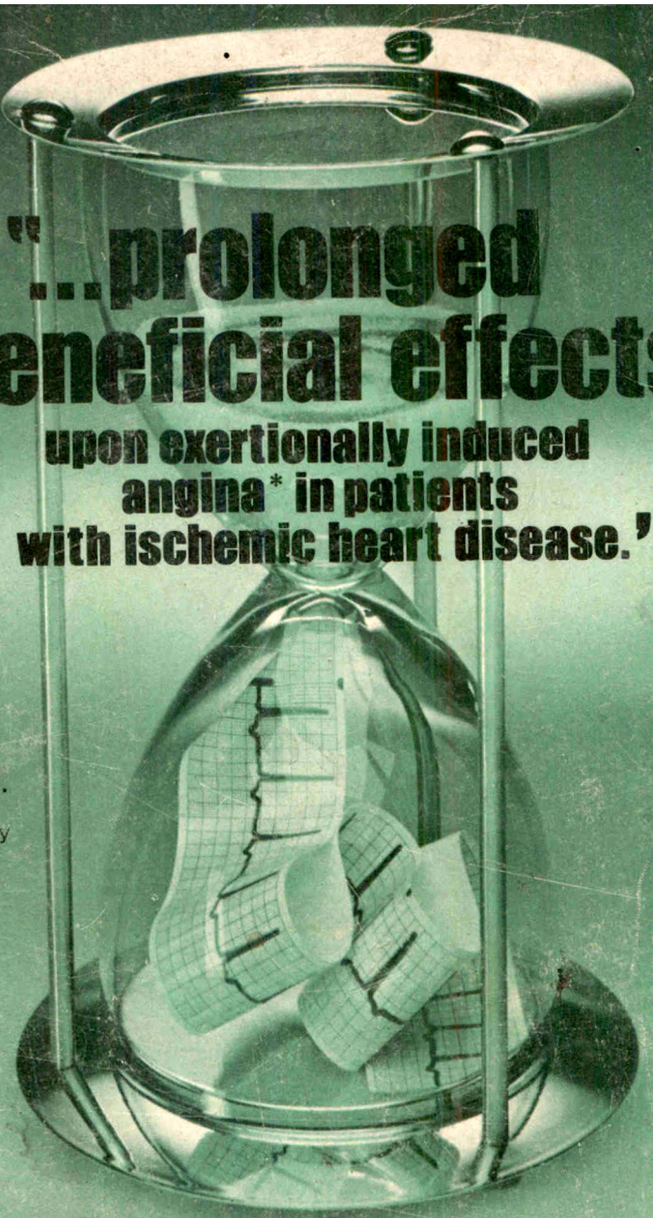
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"...prolonged beneficial effects

upon exertionally induced angina* in patients with ischemic heart disease."[1]



A double-blind, controlled study of 28 patients employing maximal treadmill exercise stress tests.

1. Antianginal efficacy of oral therapy with isosorbide dinitrate capsules. Lee G, Mason DT, Amsterdam EA, Miller RR, and DeMaria, AN. *Chest* 73:327-333, 1978.

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Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is co mon and may be severe and persistent. Transient episodes of dizziness weakness as well as other signs of cerebral ischemia associated v postural hypotension may occasionally develop. This drug can act as physiological antagonist to norepinephrine, acetylcholine, histamine, many other agents. An occasional individual exhibits marked sensitivity the hypotensive effects of nitrite, and severe responses (nausea, vomiti weakness, restlessness, pallor, perspiration and collapse) can occur ev with the usual therapeutic dose. Alcohol may enhance this effect. Drug fa and/or exfoliative dermatitis may occasionally occur.

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